CASE LA29a DIV-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

CHENG ET AL.

APPLICATION NO: Division of Application Serial No. 09/812,960 Filed March 20, 2001

FILED: Herewith

FOR: SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTIOBESITY AGENTS AND METHOD

Assistant Commissioner for Patents
Washington, D.C. 20231

PREEXAMINATION AMENDMENT

Sir:

Please amend the above-identified application to read as follows.

In the Specification:

Page 1, line 4, after "this" and before "is", please insert -- is a division of U.S. application Serial No. 09/812,960 filed March 20,2001, which --

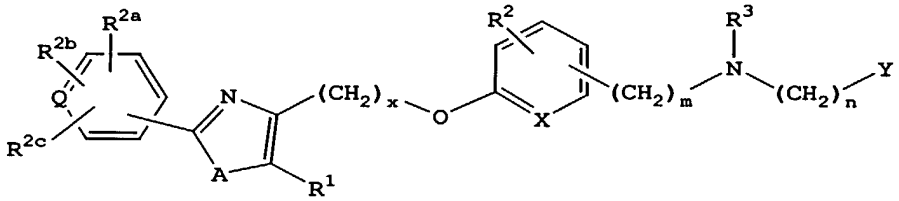
line 5, after "2000" and before "which", please insert -- , now abandoned, -- .

In the Claims:

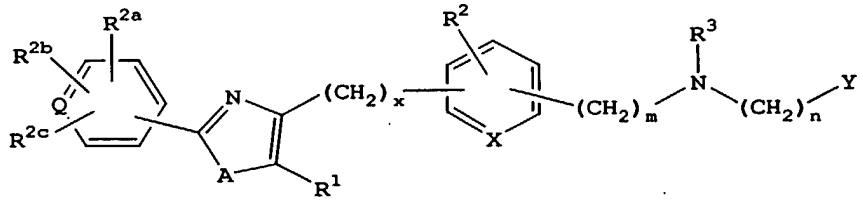
Please cancel Claims 1, 6 to 9, 11 to 13, 15, 19, 23 to 25, 29, 33, 35, 36, 38, 41 to 49 and 51 to 54.

Please amend Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 30 to 32, 34, 37, 39, 40 and 50 as follows.

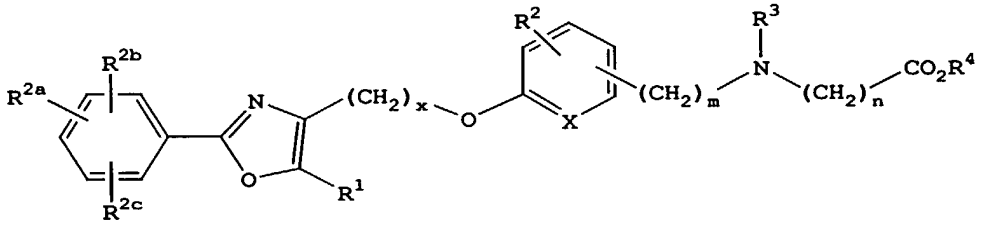
--2. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



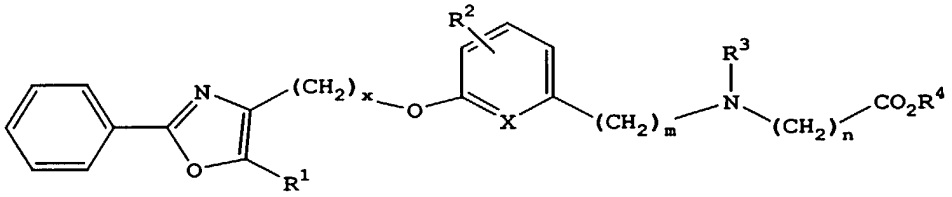
or



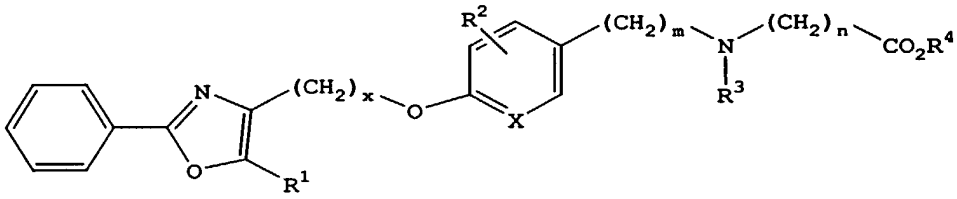
--3. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



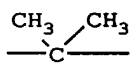
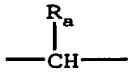
--4. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



or

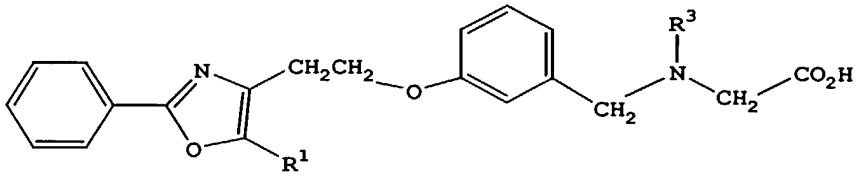


--5. (Amended) The method as defined in Claim 34 where in the compound employed $(CH_2)x$ is alkylene, alkenylene, allenyl, or alkynylene. --

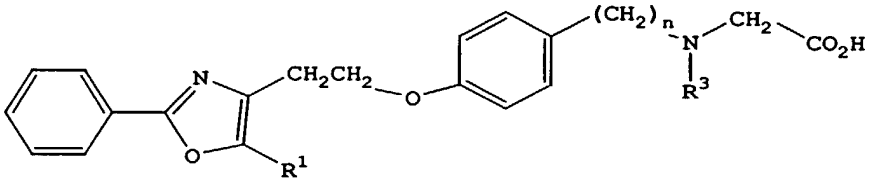
--10. (Amended) The method as defined in Claim 34 where in the compound employed $(CH_2)_x$ is CH_2, $(CH_2)_2$, $(CH_2)_3$, or  , $(CH_2)_m$ is CH_2, or  where R_a is alkyl or alkenyl, $(CH_2)_n$ is CH_2, R^1 is lower alkyl, R^2 is H, R^{2a} is H, R^4 is H, and R^3 is arylalkyloxycarbonyl,

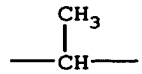
aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted. --

--14. (Amended) The method as defined in Claim 34 where the compound employed has the structure

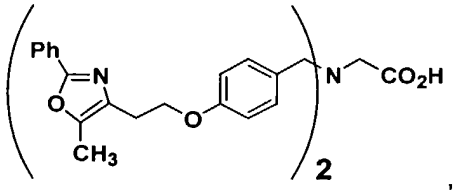


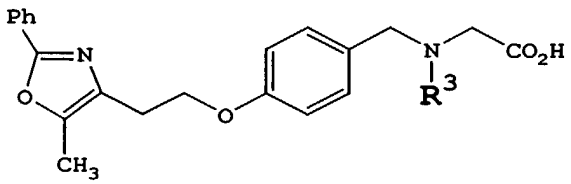
or



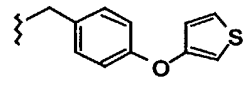
where $(CH_2)_n$ is CH_2 or  . --

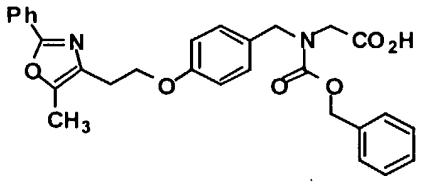
--16. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

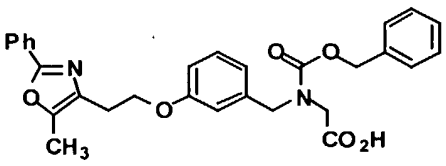


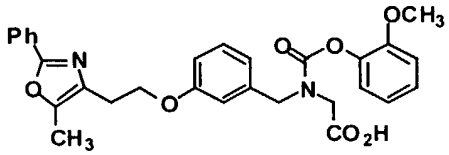


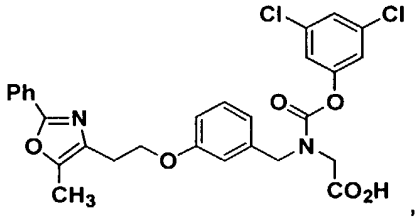
, where R^3 =

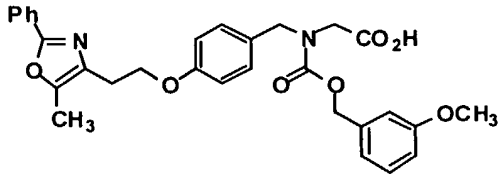


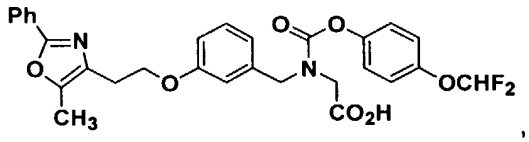


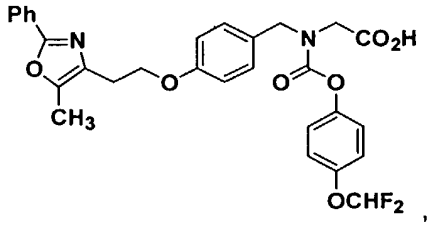


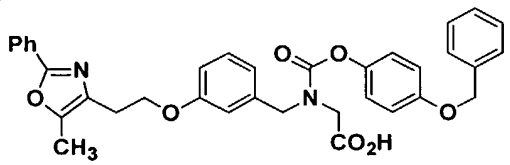


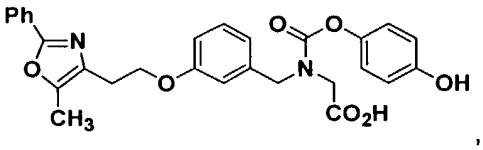












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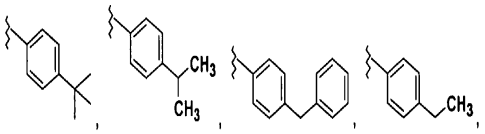
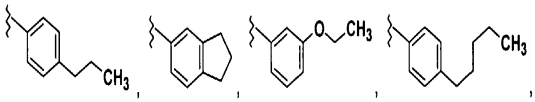
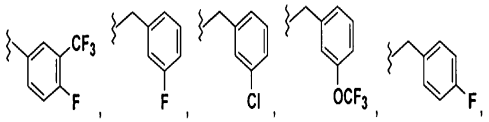
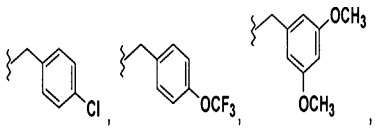
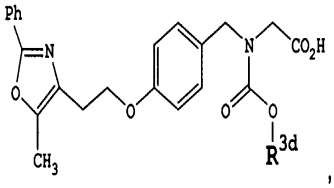


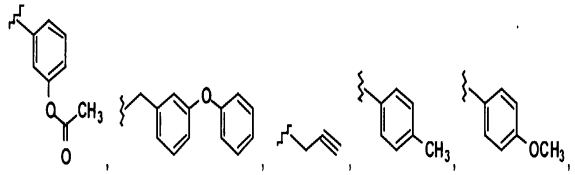


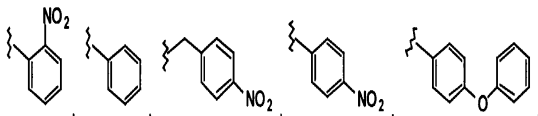


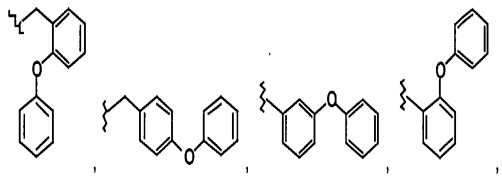


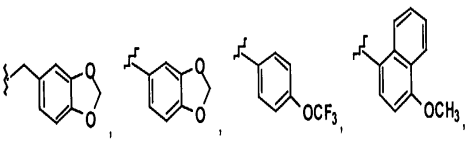


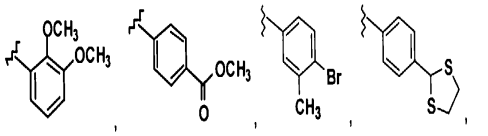
, where R^{3d} =

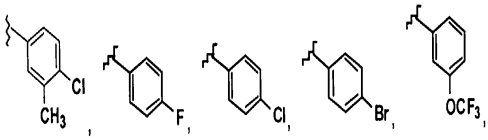


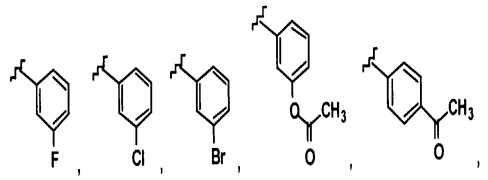


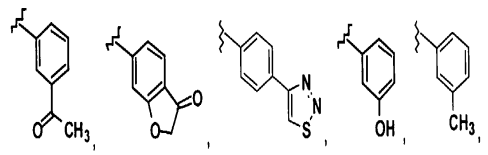


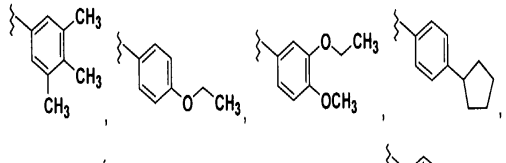


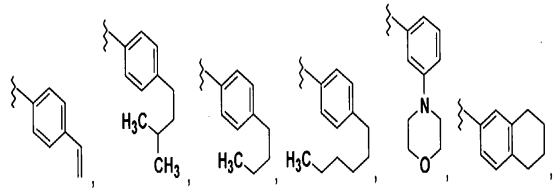


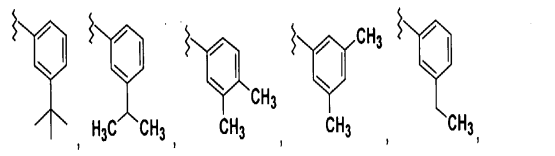


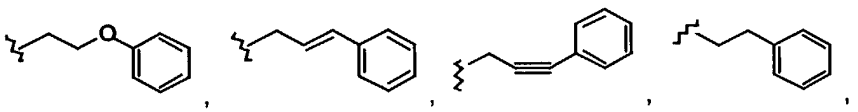


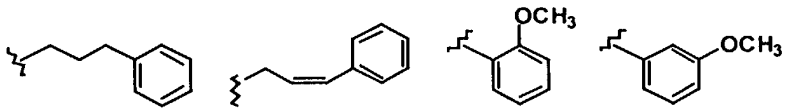


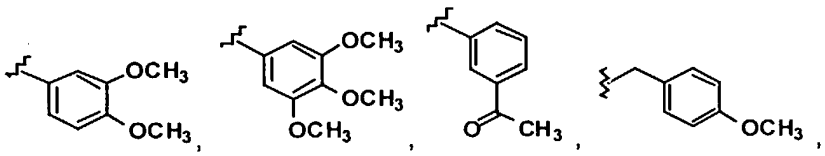


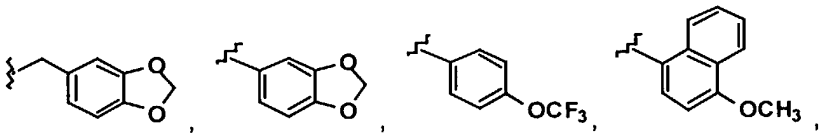


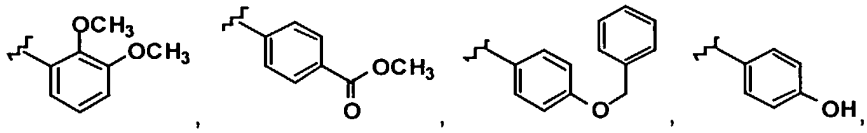


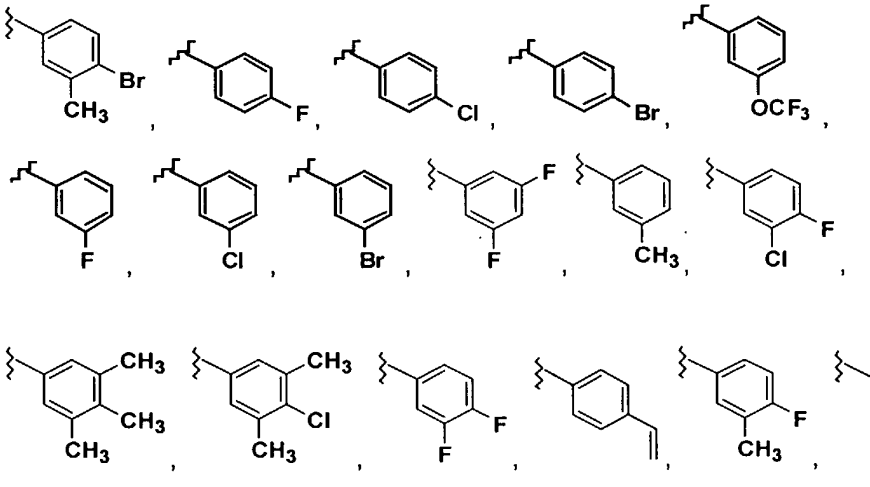


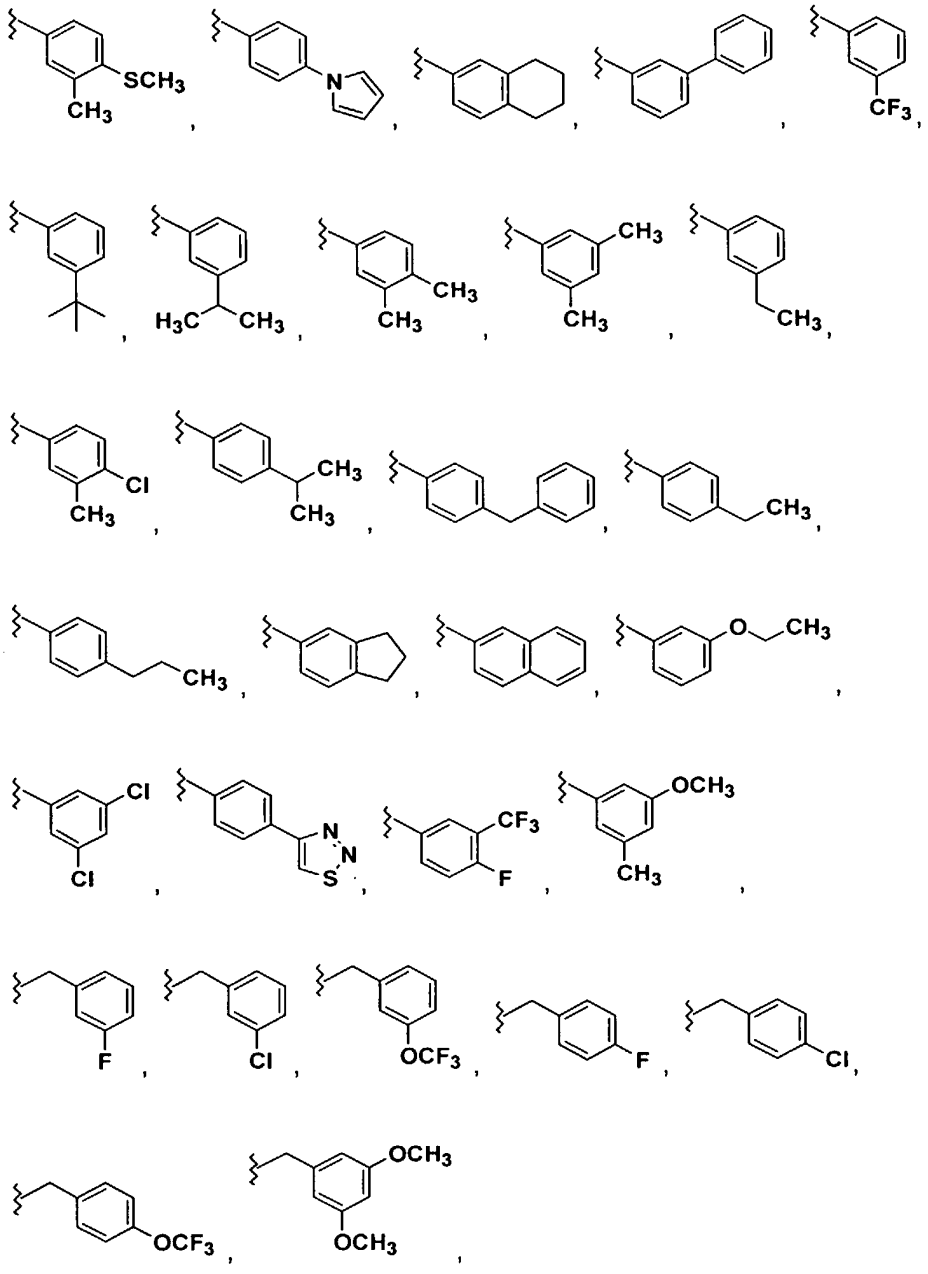


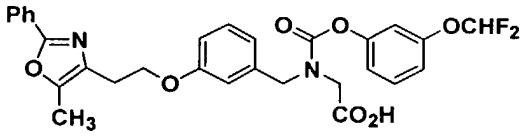









SCH3
CH3
N
CF3
H3C
CH3
Cl
O
OCH3
F
OCF3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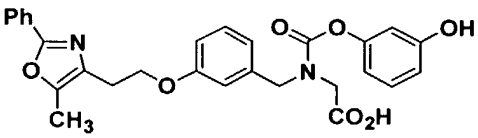
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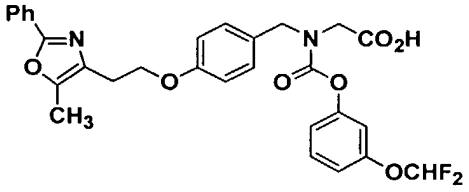
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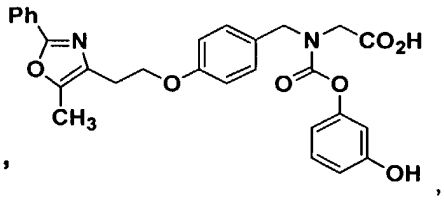
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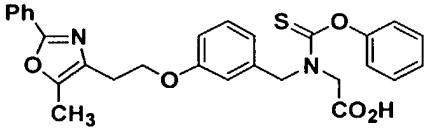
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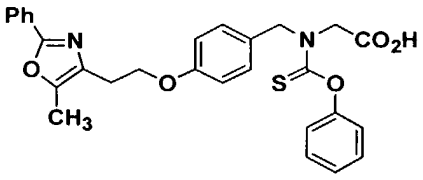
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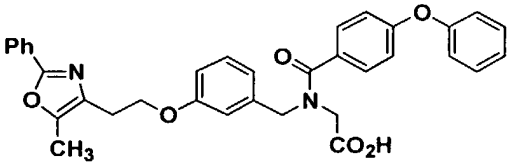
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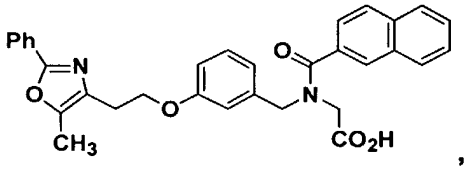
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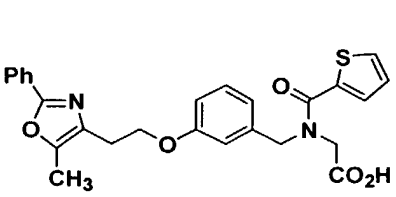
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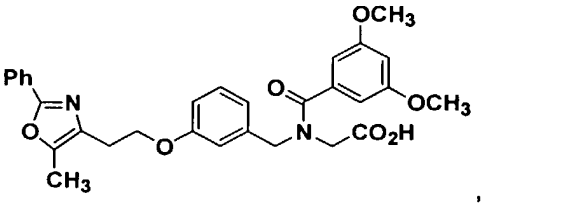
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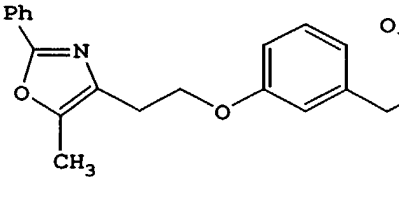
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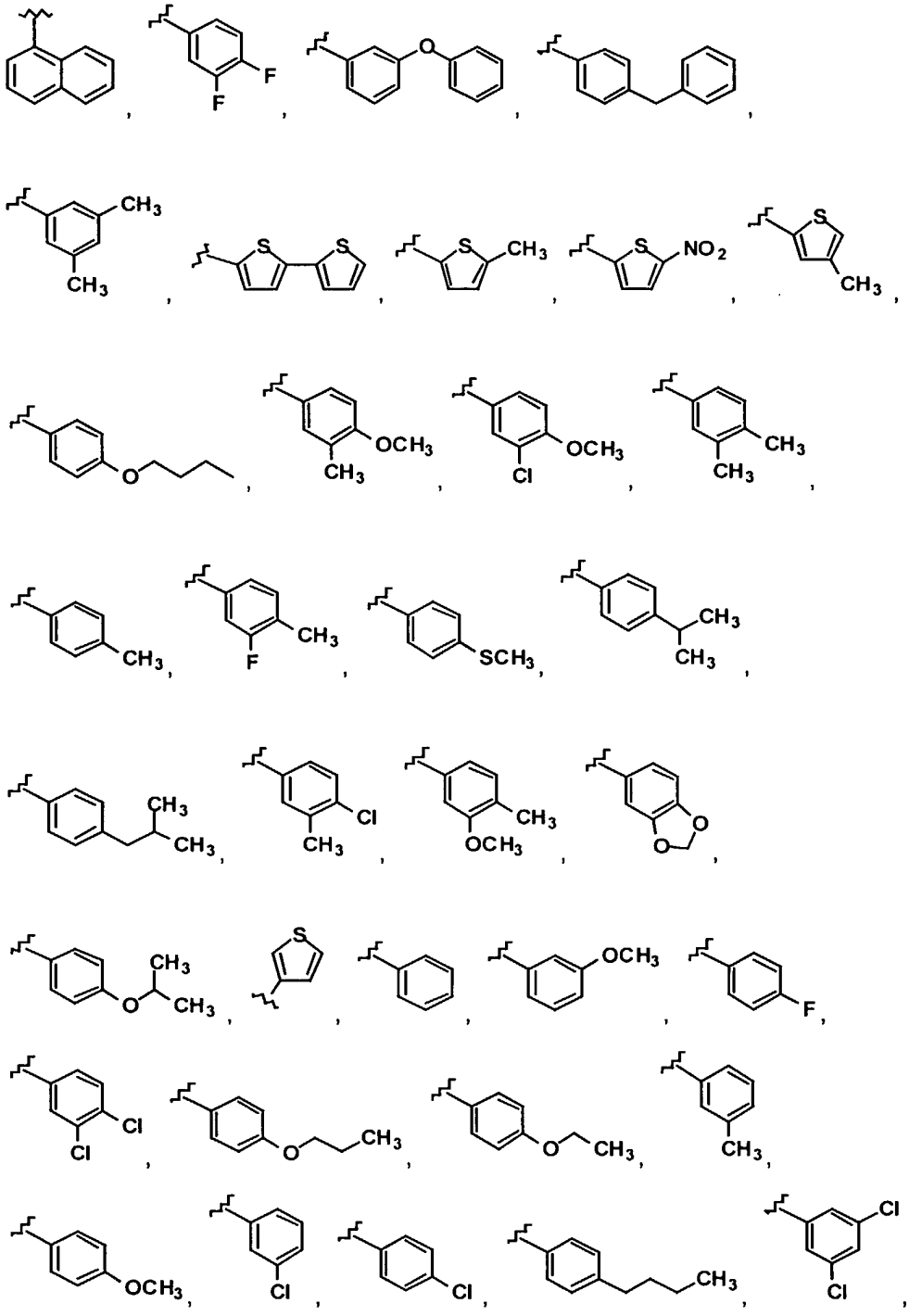

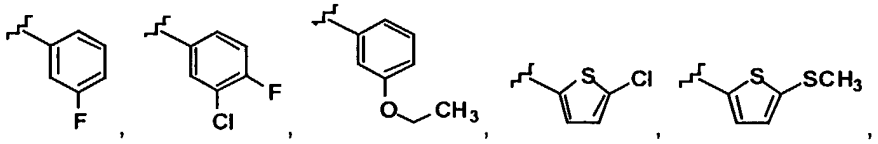

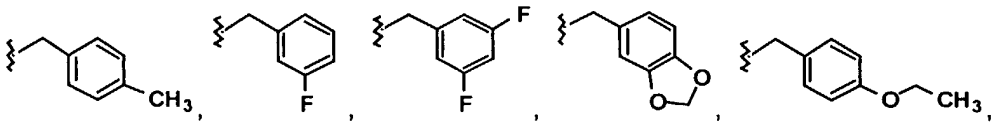

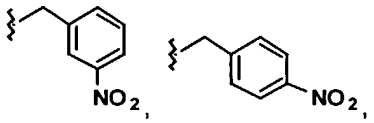

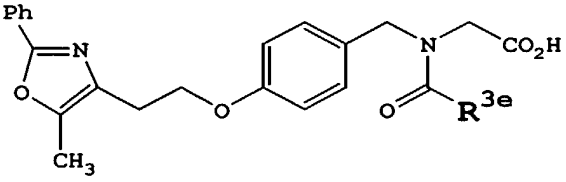

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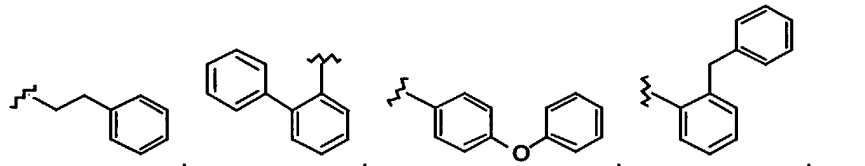

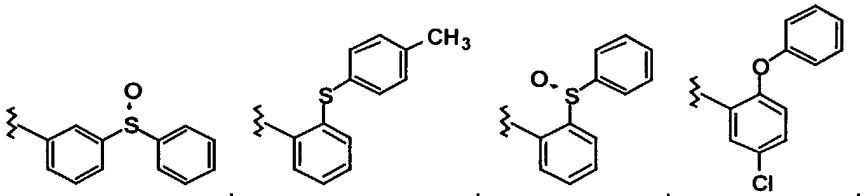

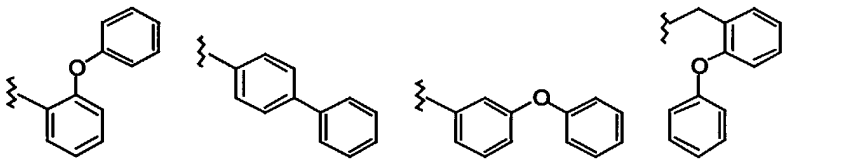

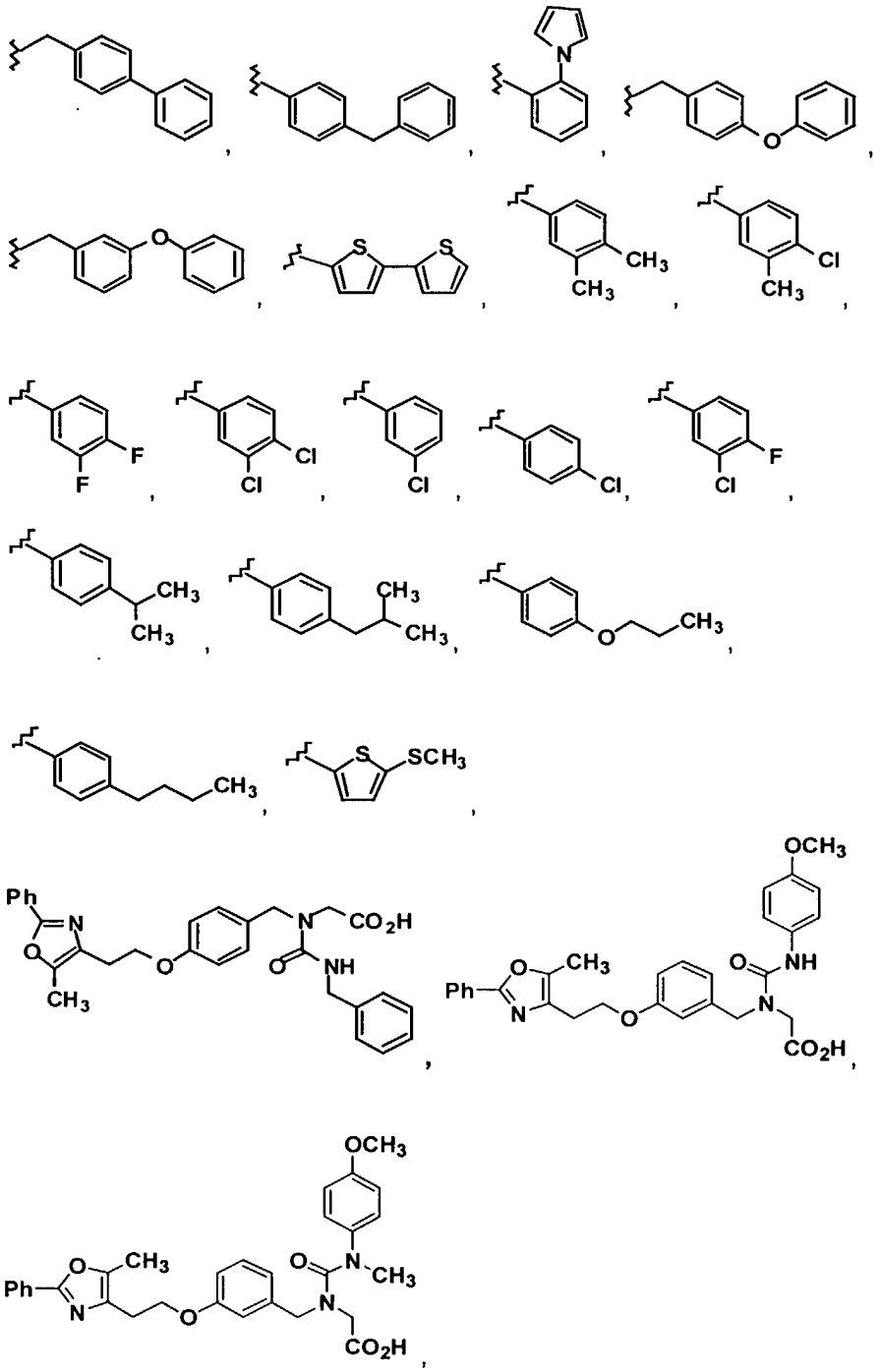

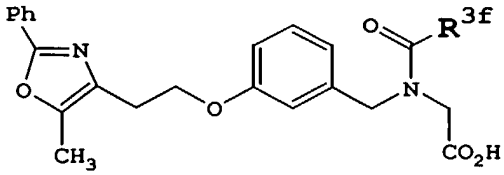

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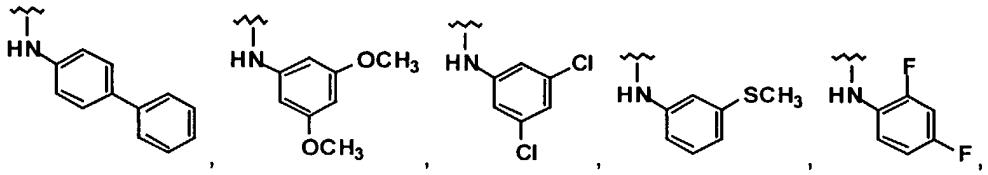

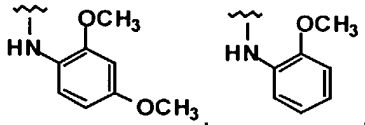

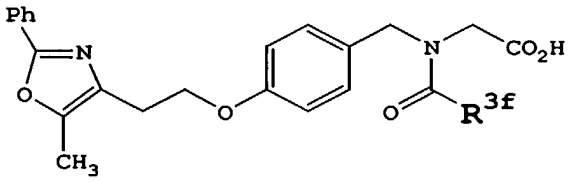

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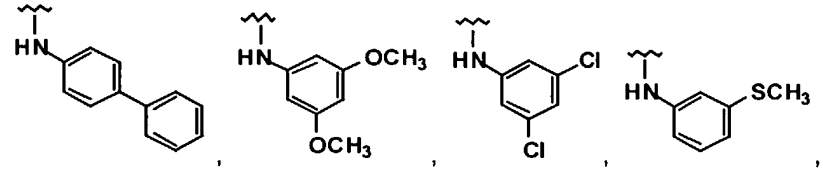

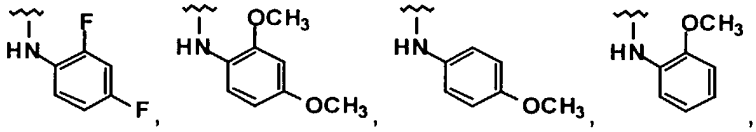

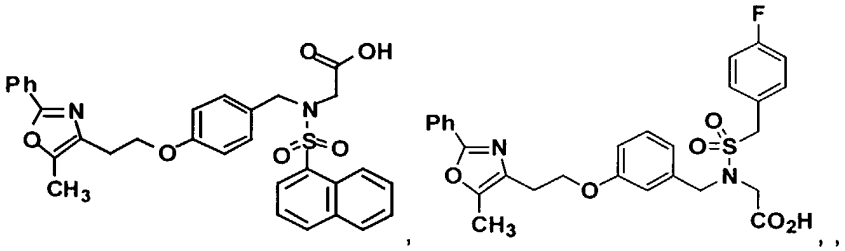

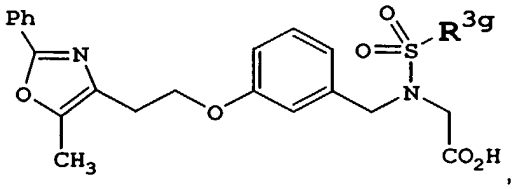

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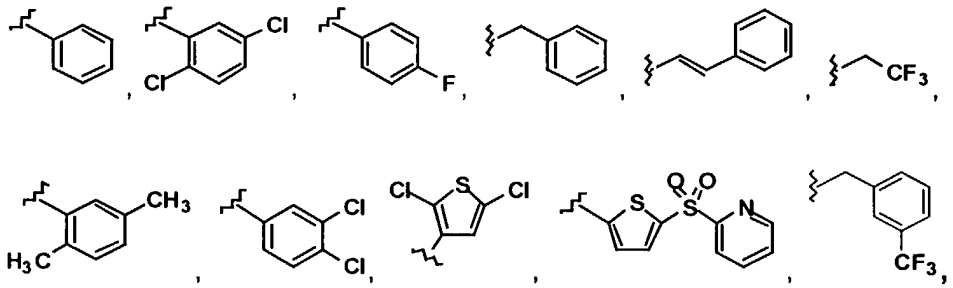

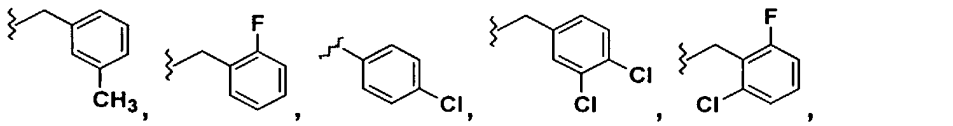

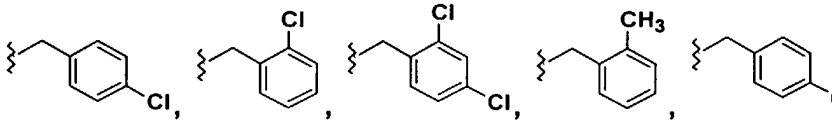

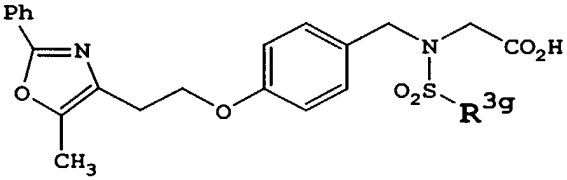

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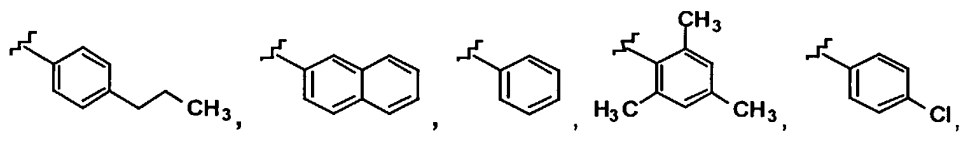
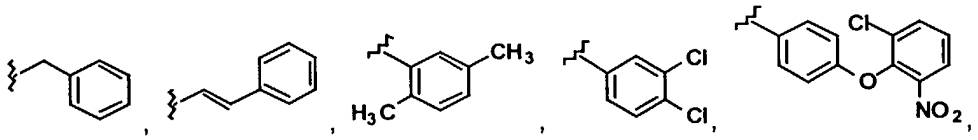
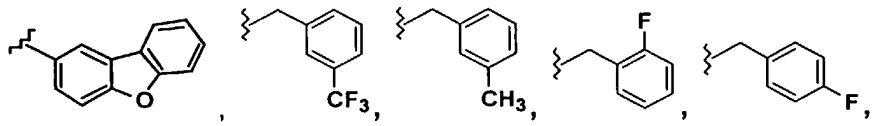
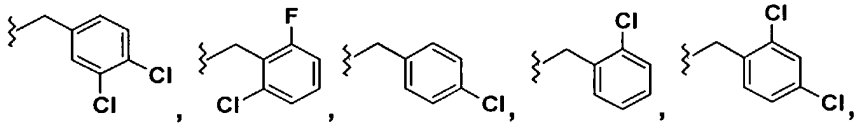
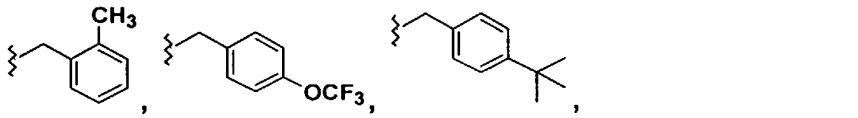
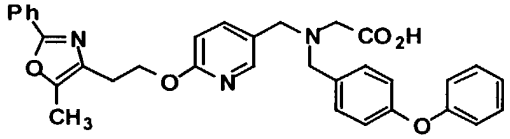


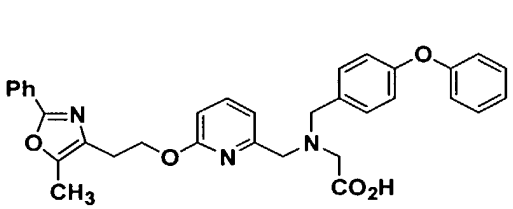


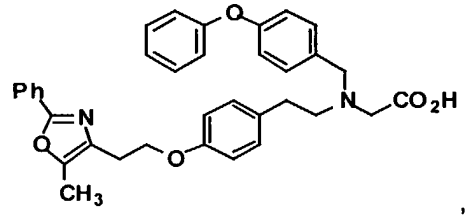


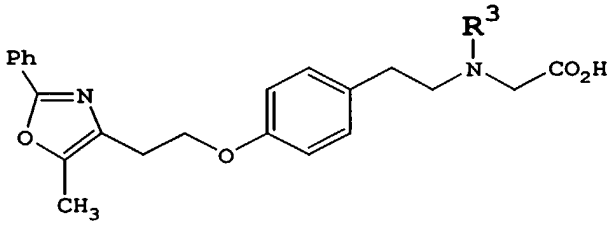




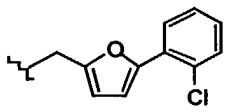
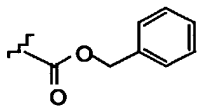
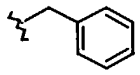


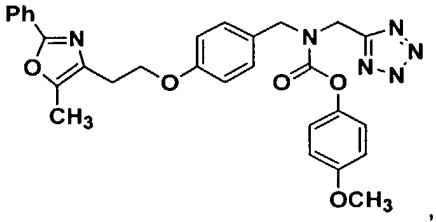
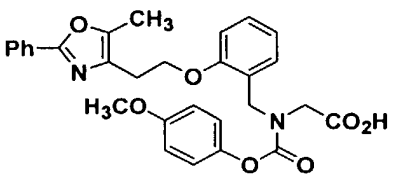


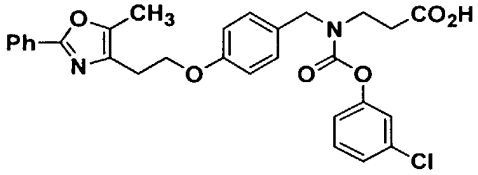
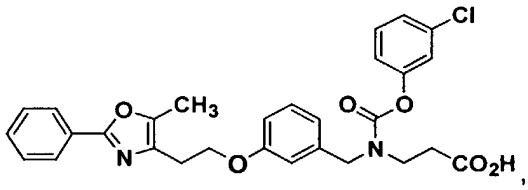


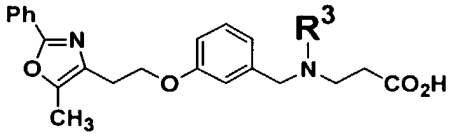


, where R^3 =

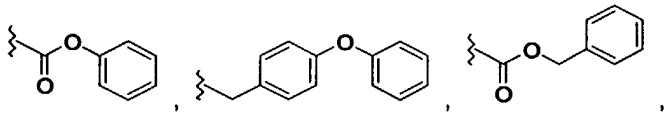




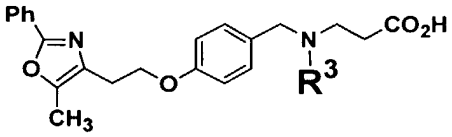





where R^3 =





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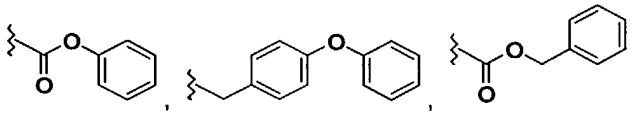
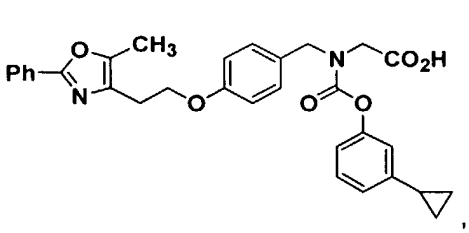
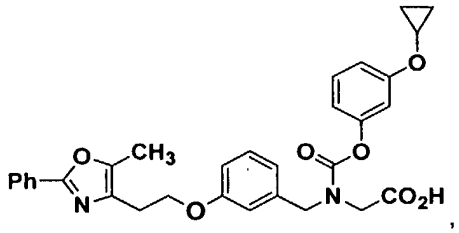
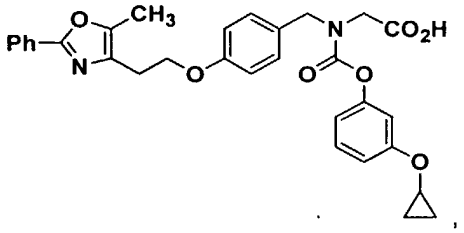
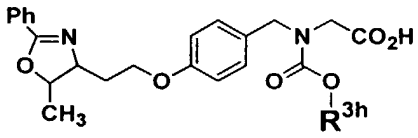
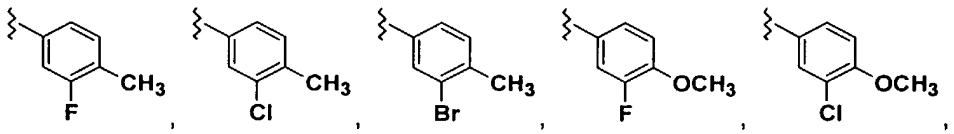
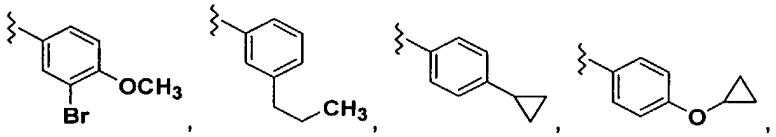
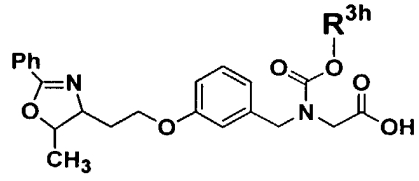



, where R^{3h} =



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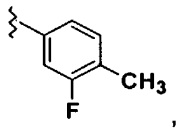
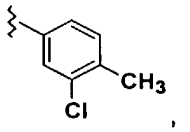
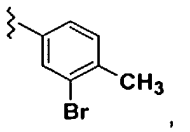
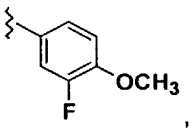
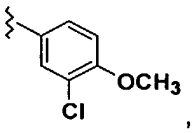
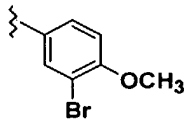
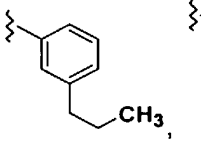
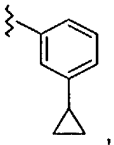
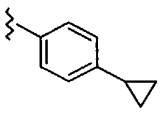
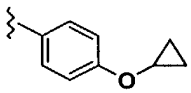
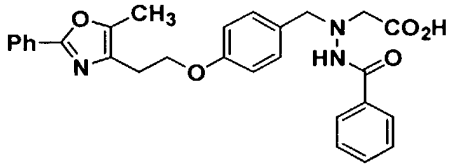
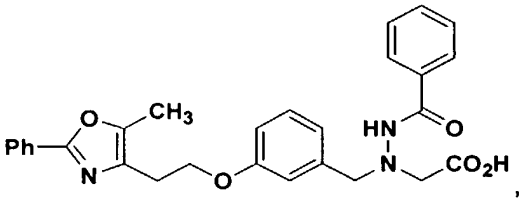
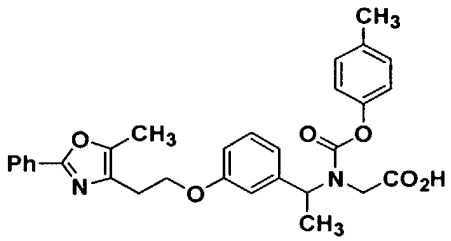
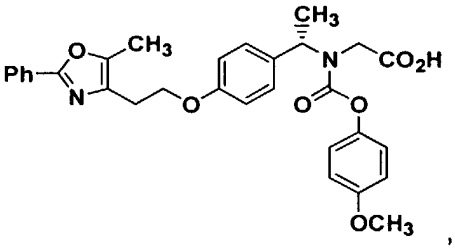
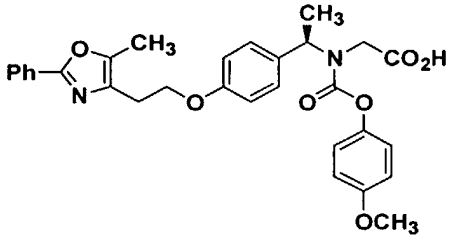
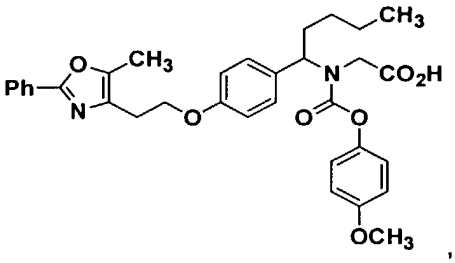
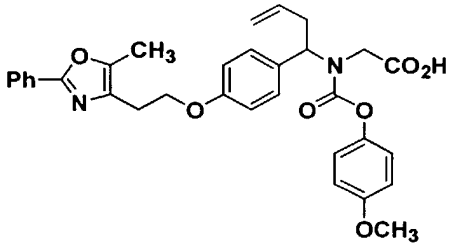
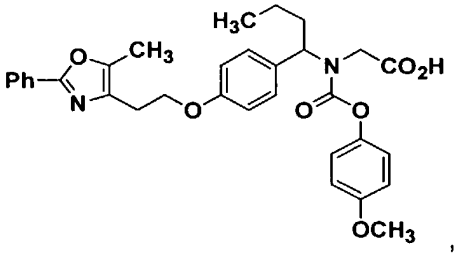

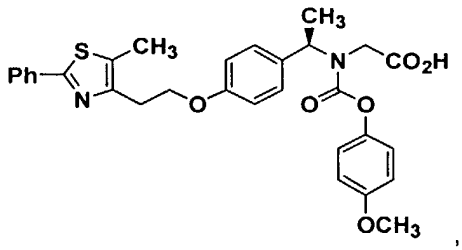
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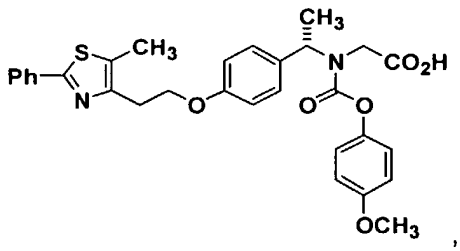
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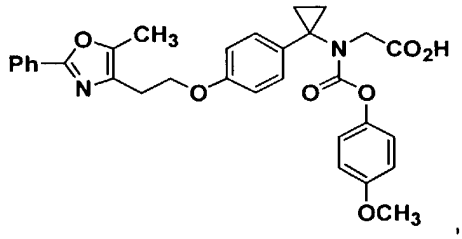
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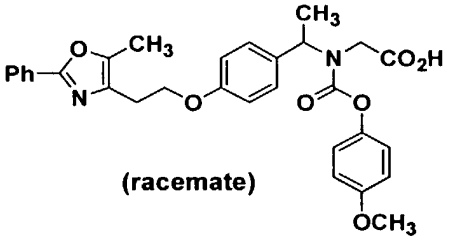
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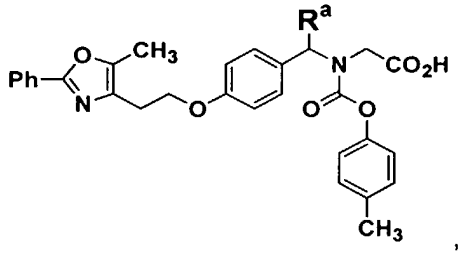
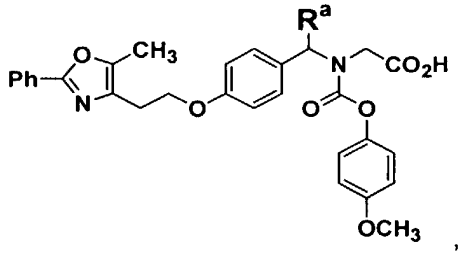
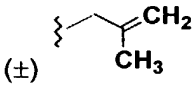

, **where R^a = (±)-Me , (±) n-Bu ,**


, **where R^a =** (±) Et, (±) i-Bu,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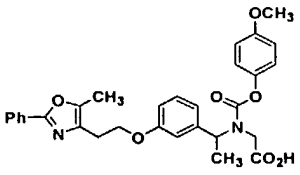
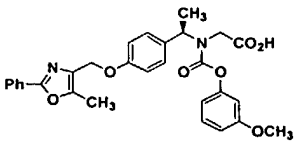
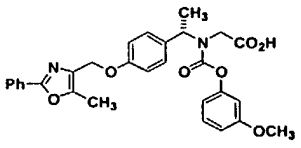

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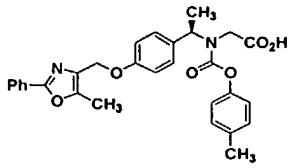
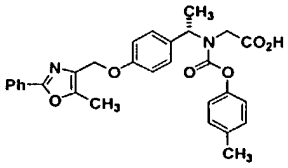
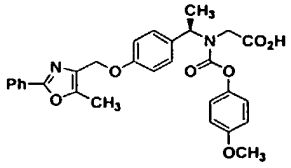
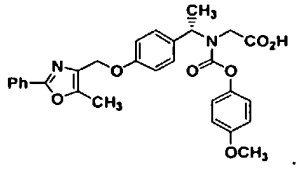
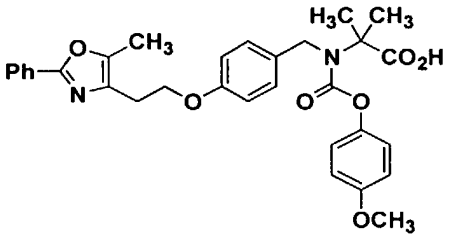

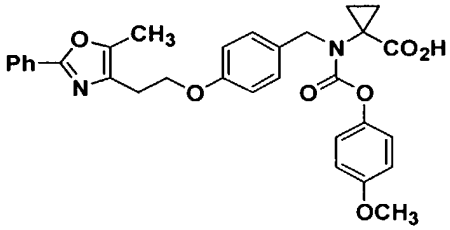
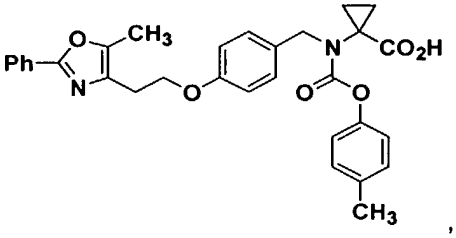

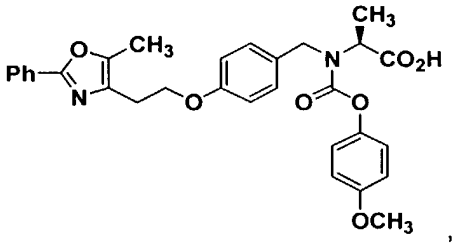
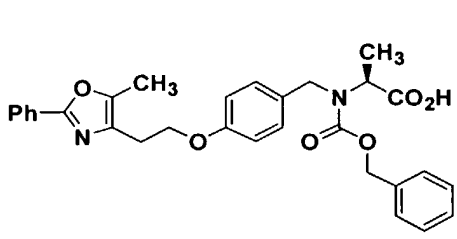

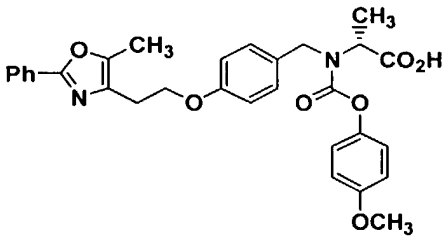

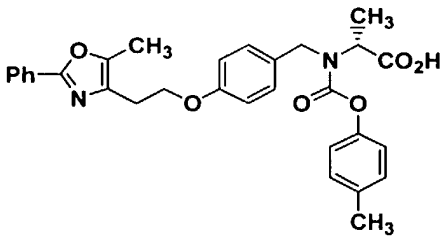

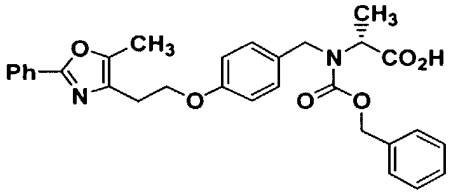

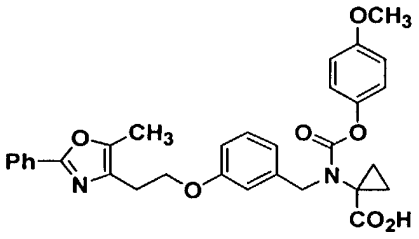

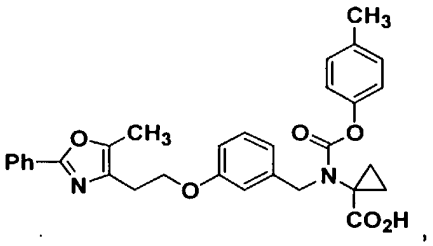

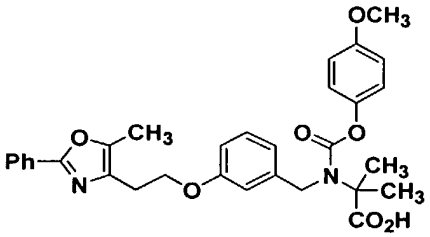

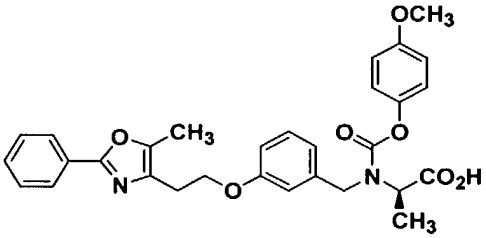

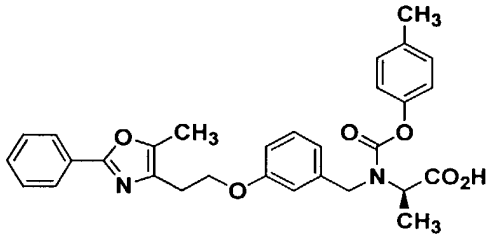

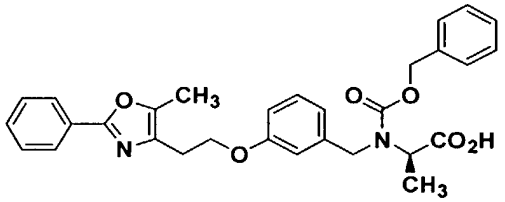

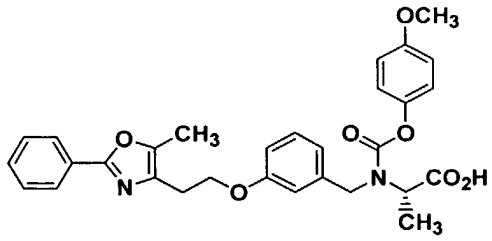

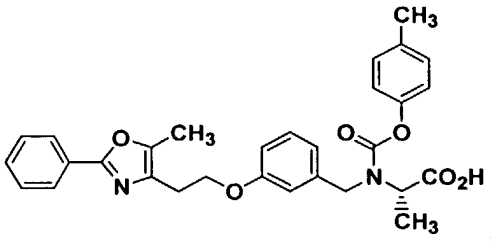

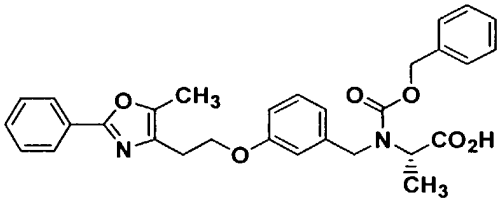

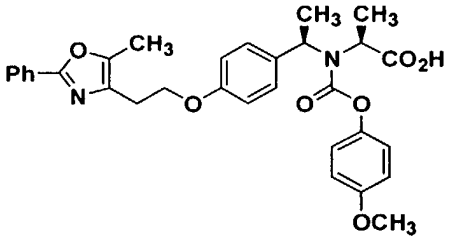

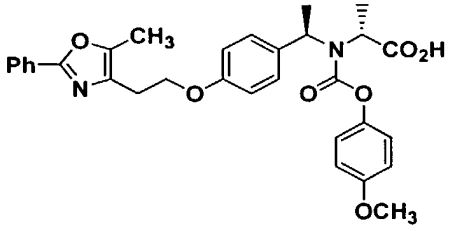

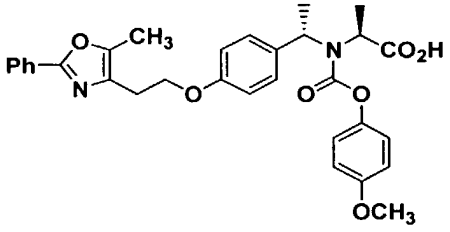

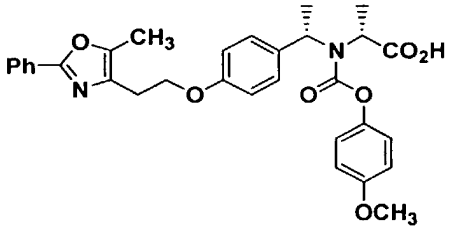

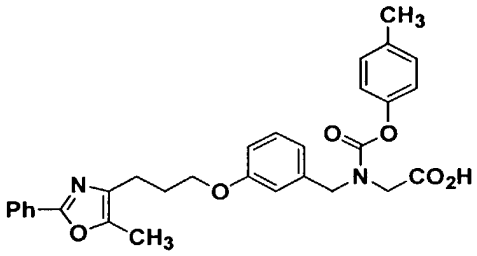

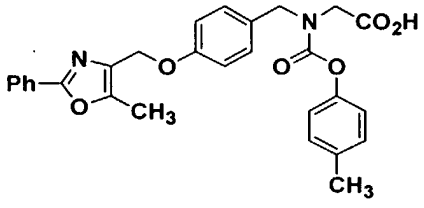

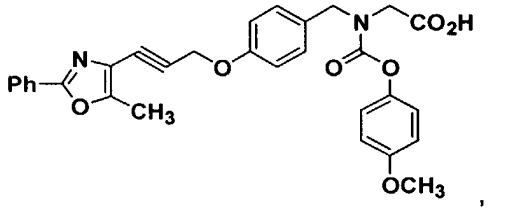

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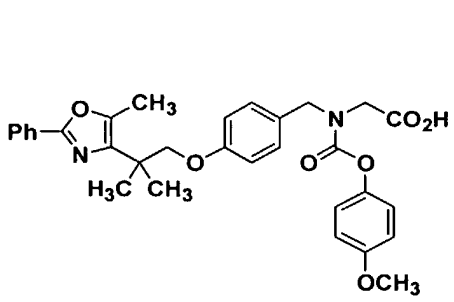
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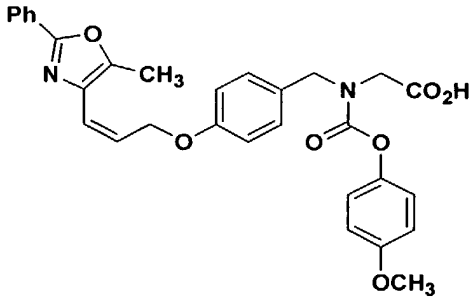
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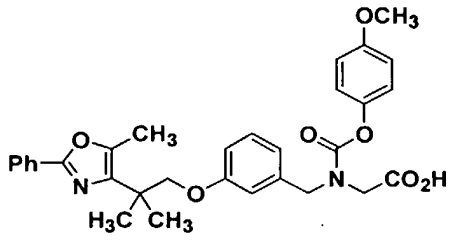

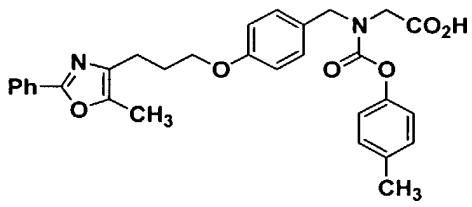
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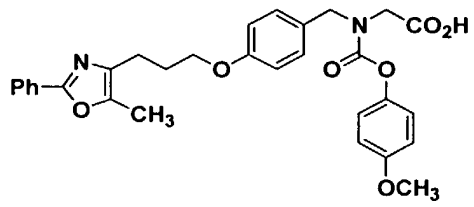
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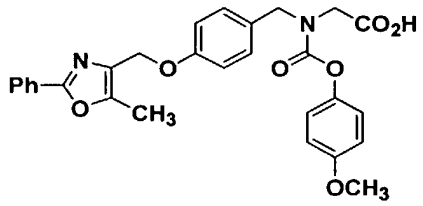
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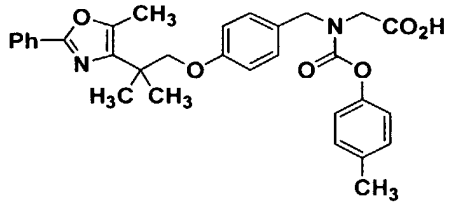

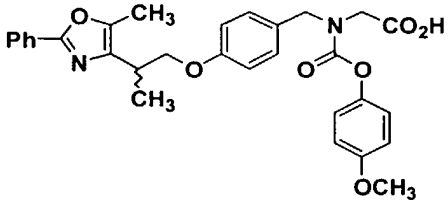
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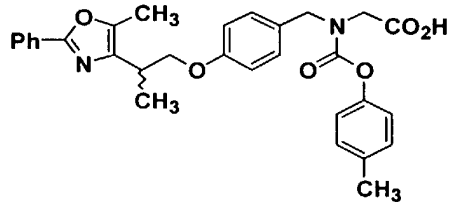

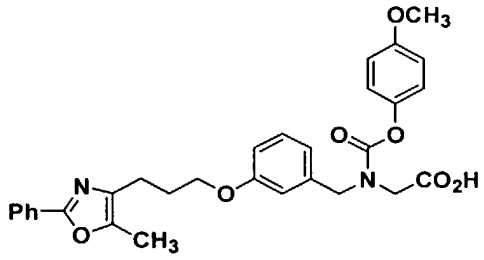
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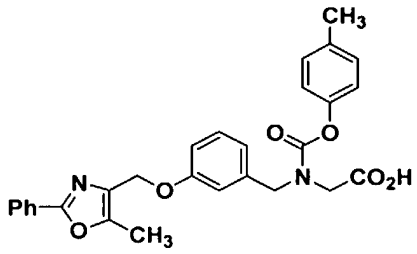
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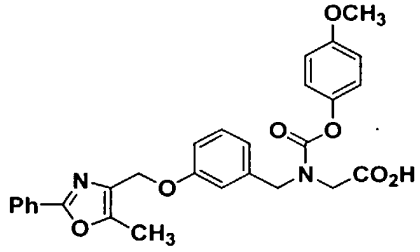
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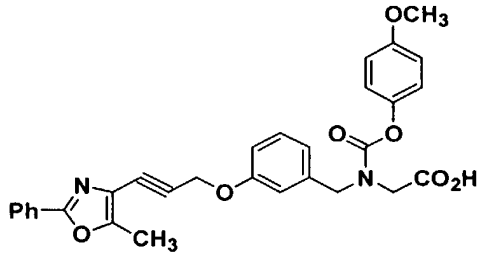
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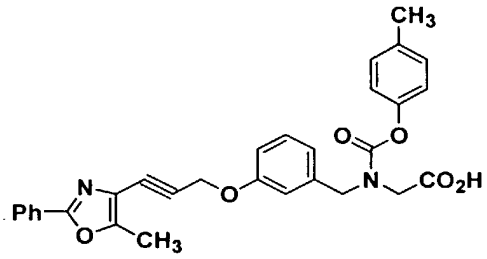
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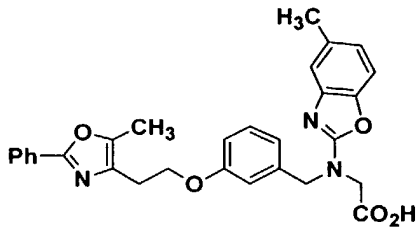
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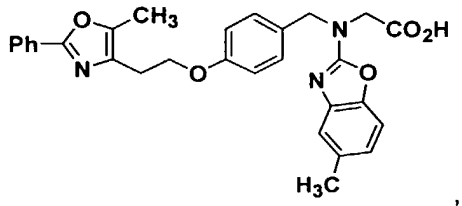
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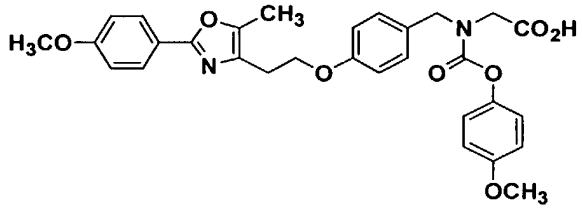
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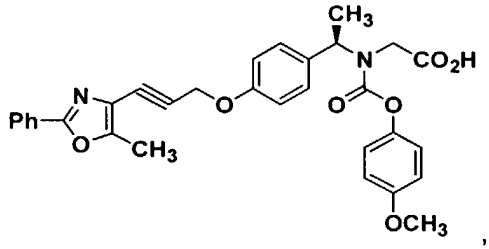
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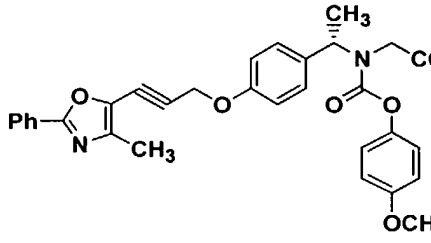
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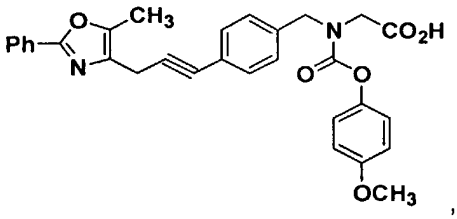
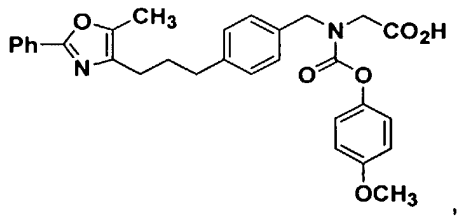
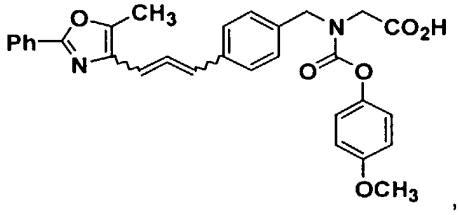
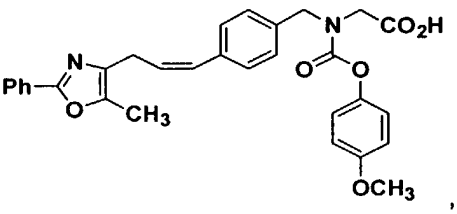
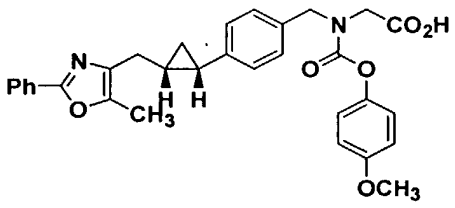
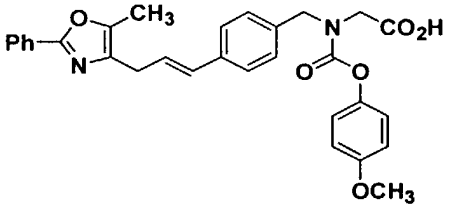


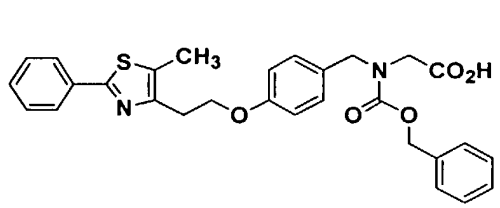


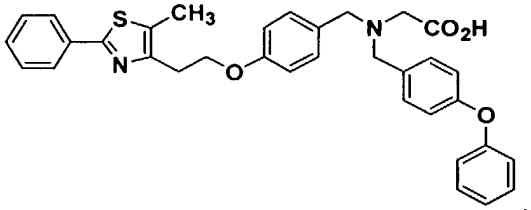


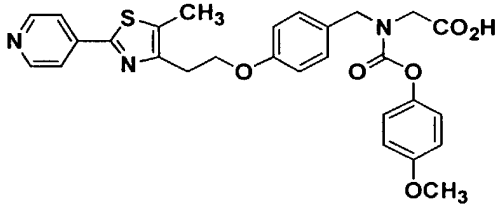


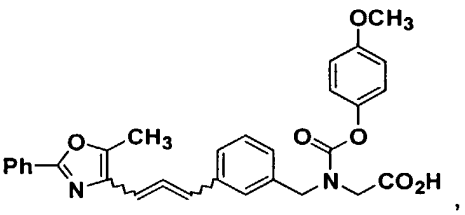


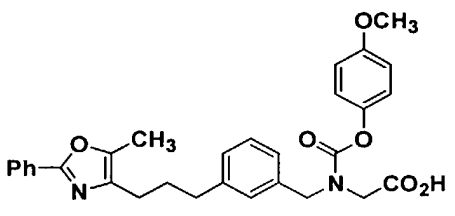


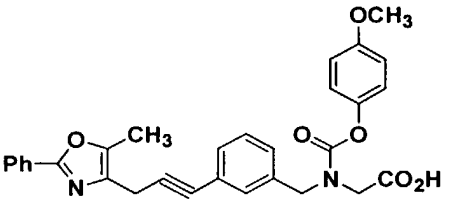


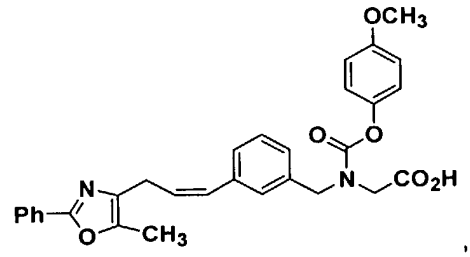
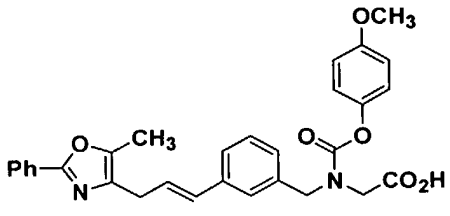
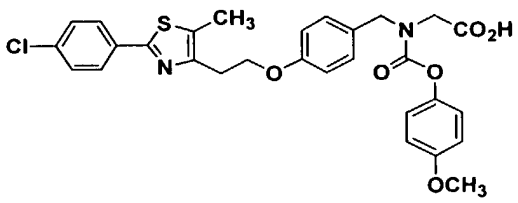
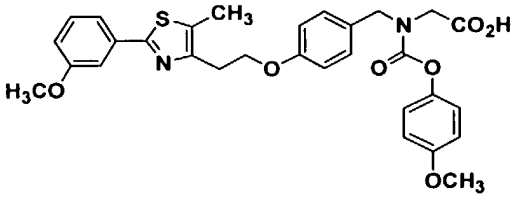
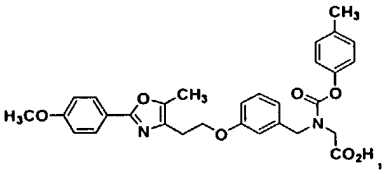
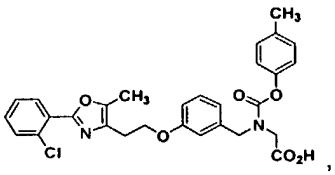
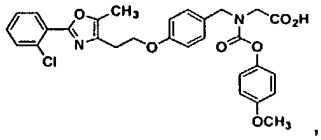
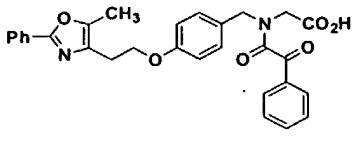
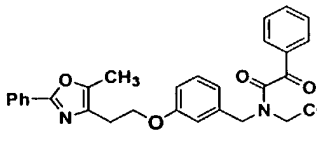


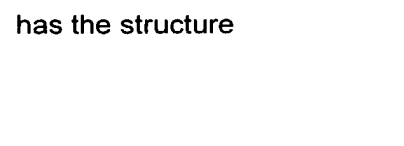




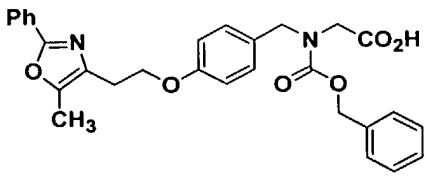


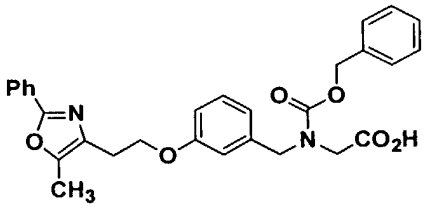


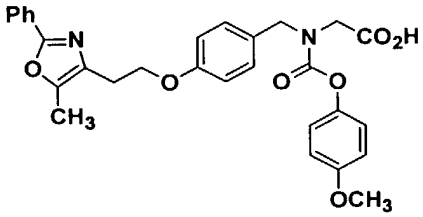










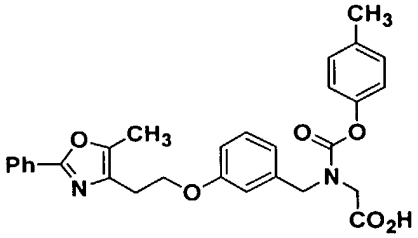



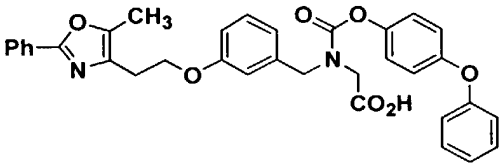
--17. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

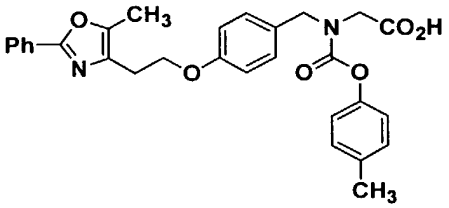


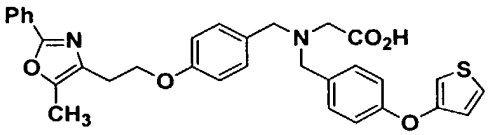


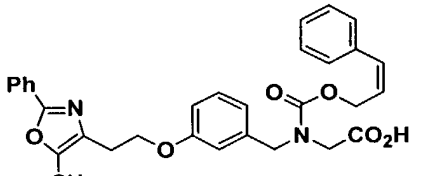


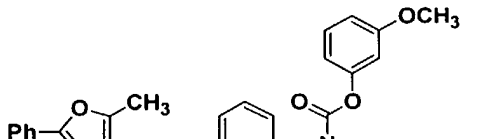


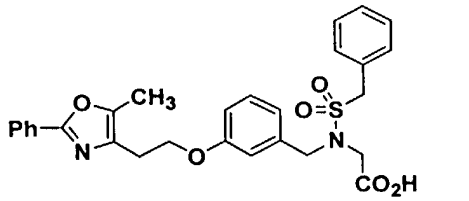


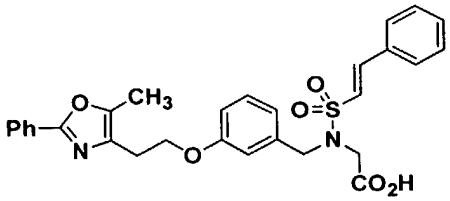


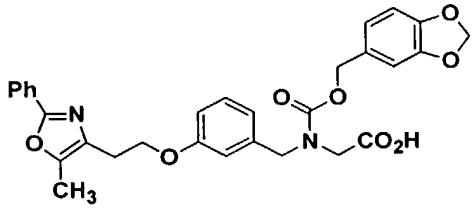


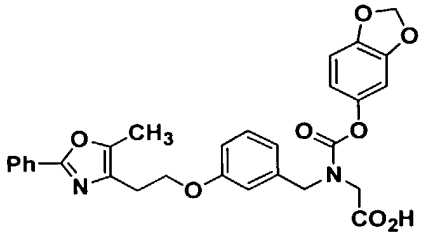


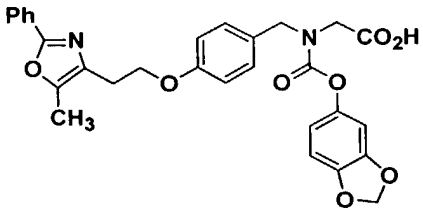


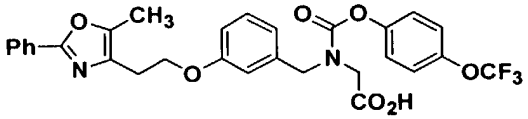


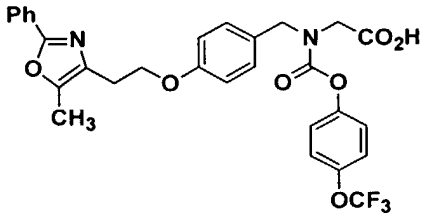


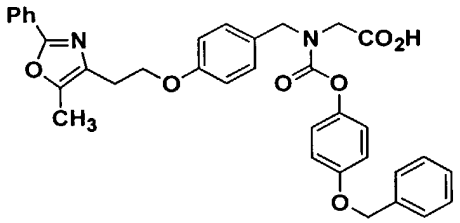


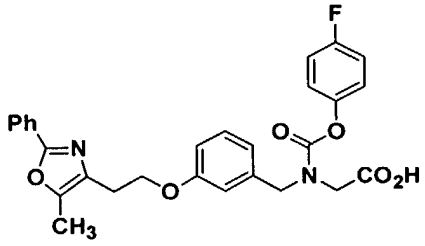


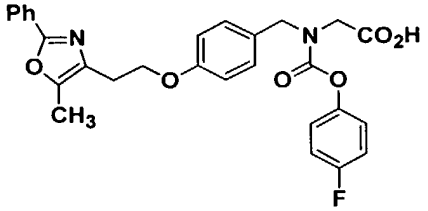


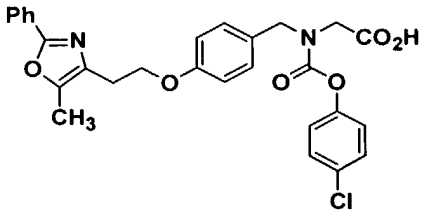


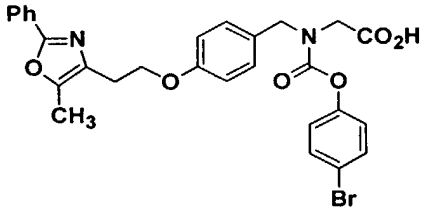


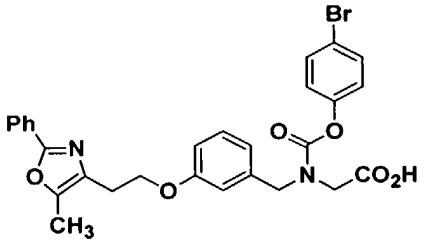


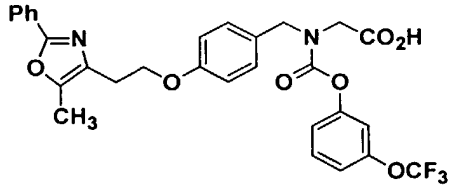


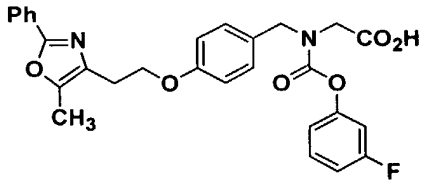


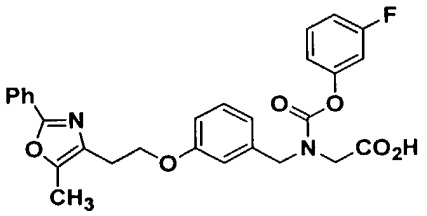


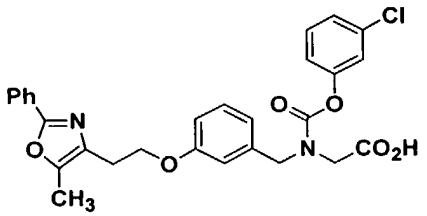


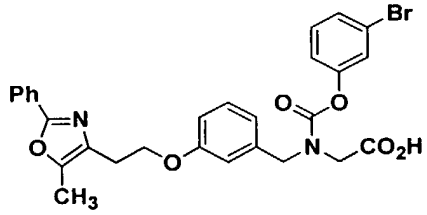


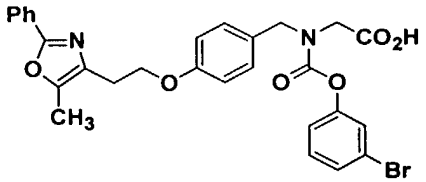


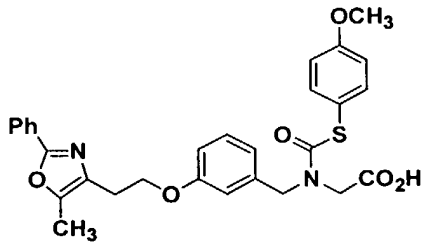


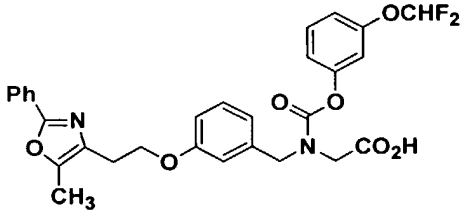


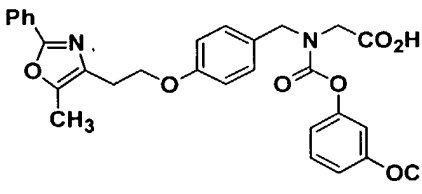


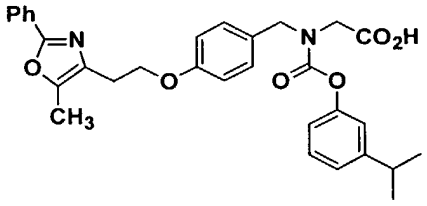


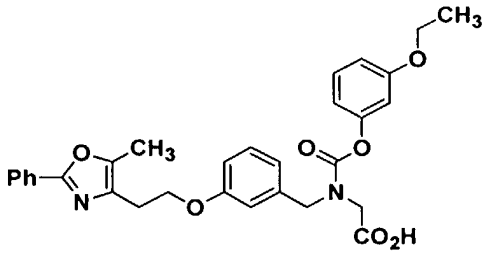


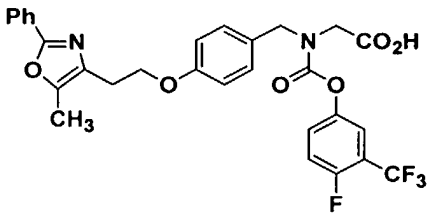


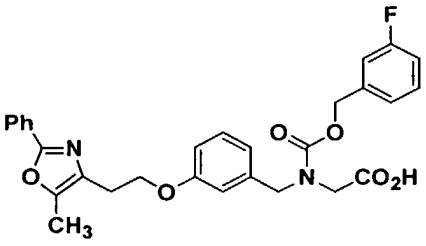


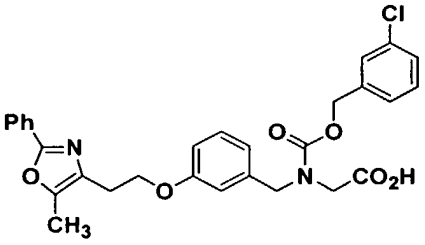


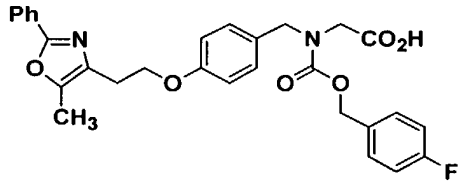


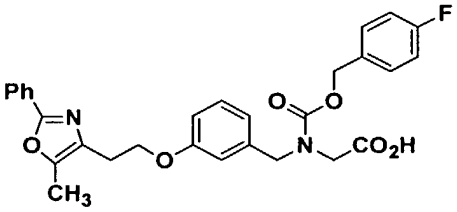


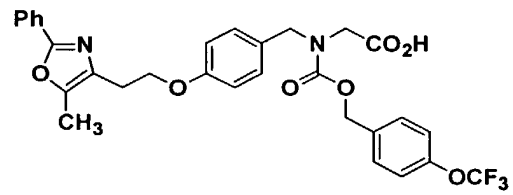


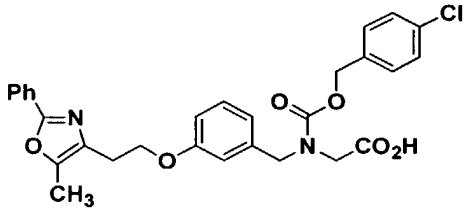


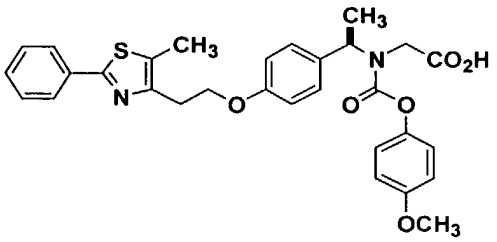


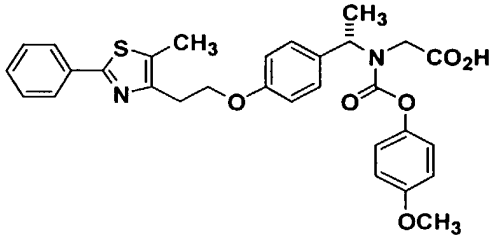


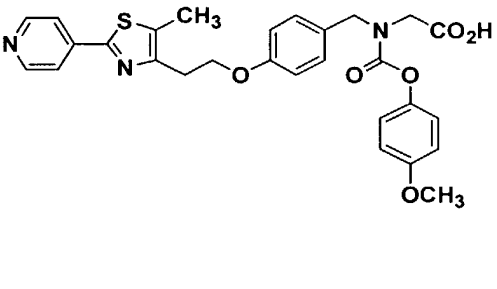












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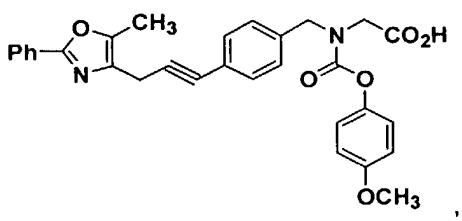
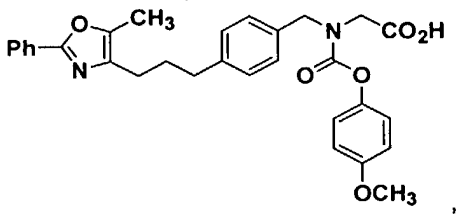
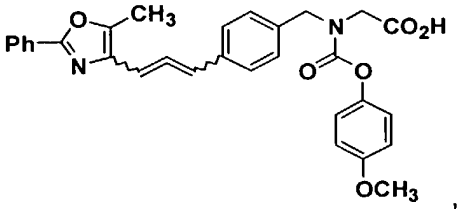
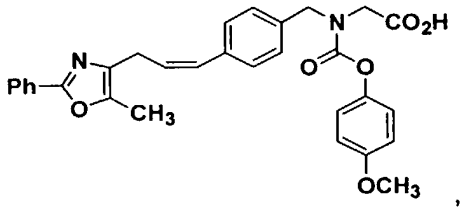
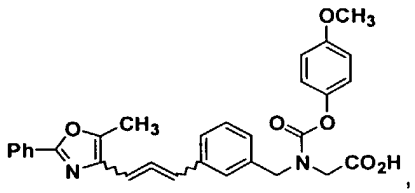
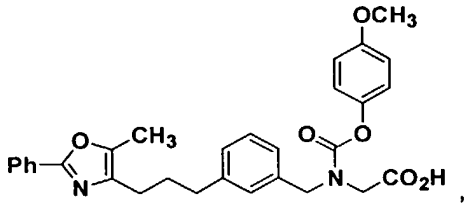
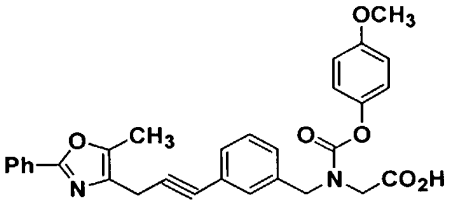
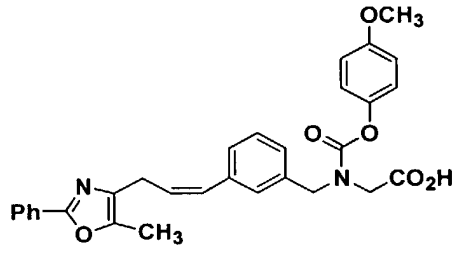
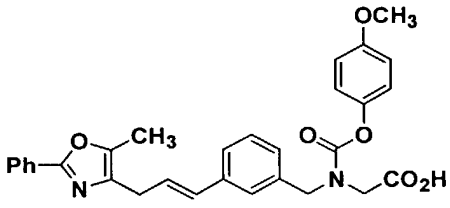
--18. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure

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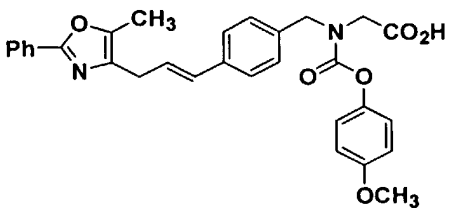

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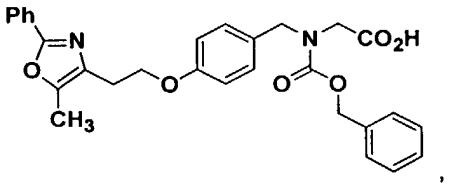
--20. (Amended) The method as defined in Claim 34 wherein the compound employed has the structure



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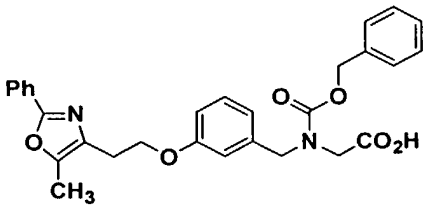

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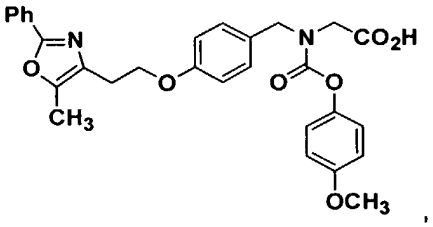

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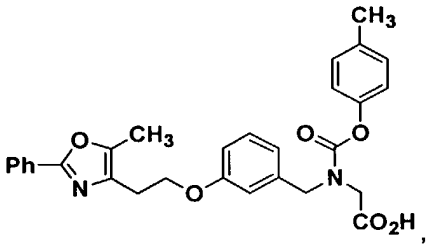

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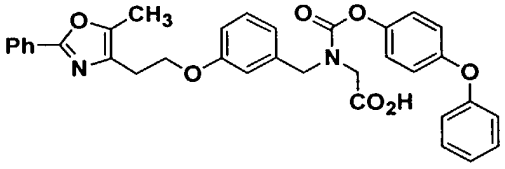

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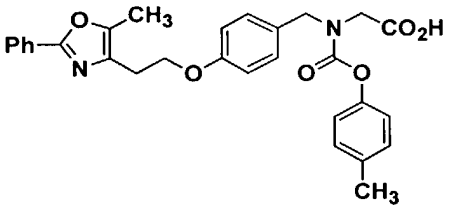

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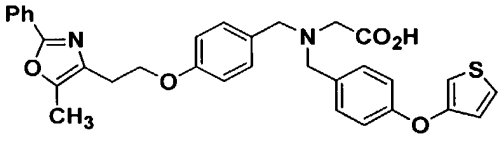

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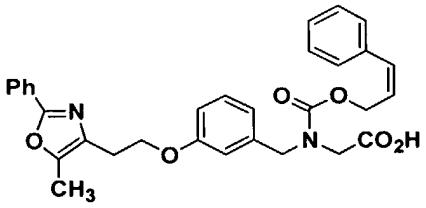

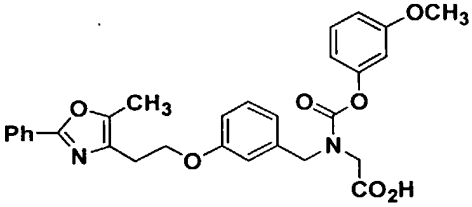

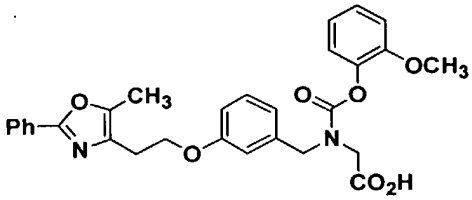

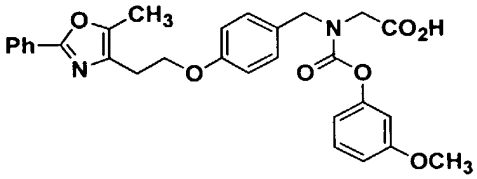

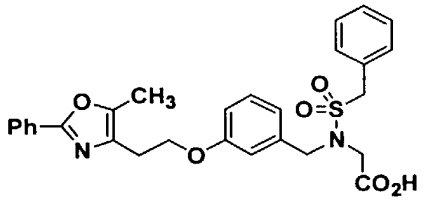

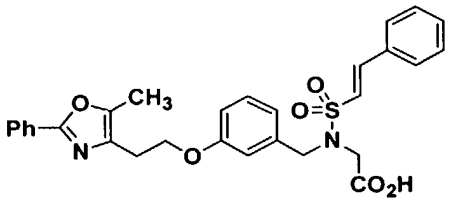

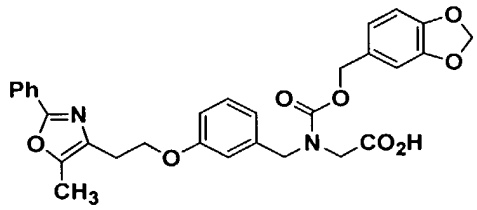

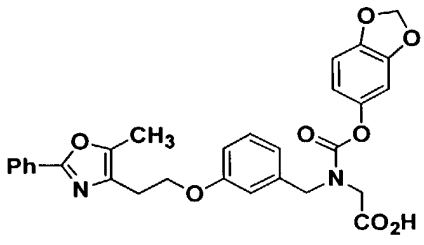

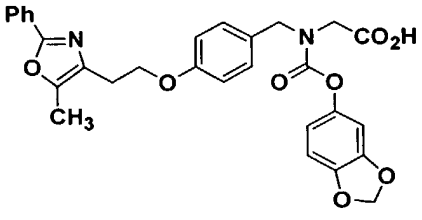

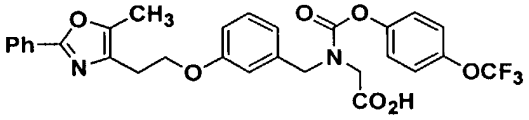

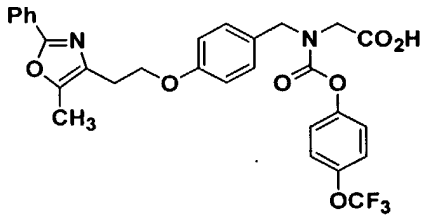

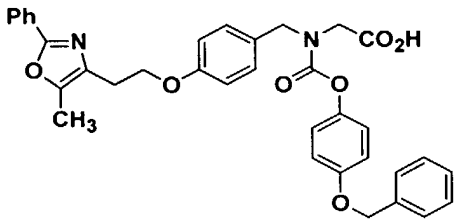

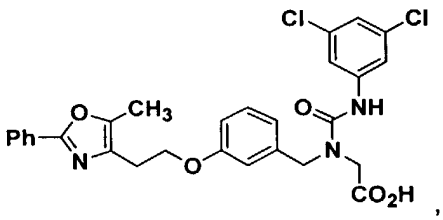

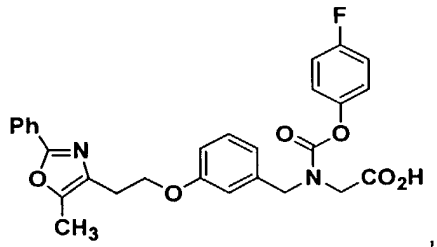

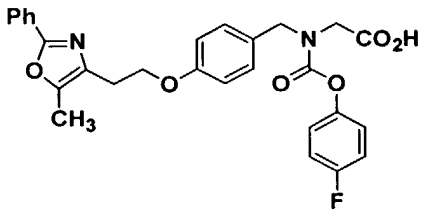

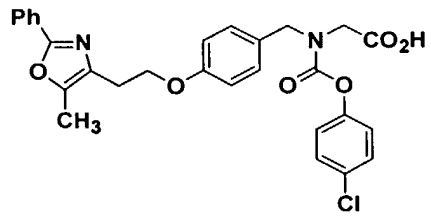

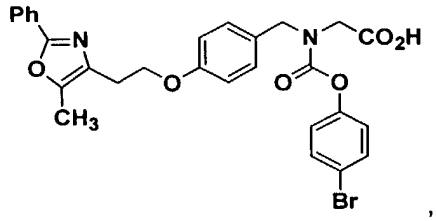

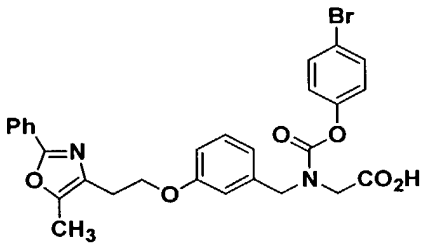

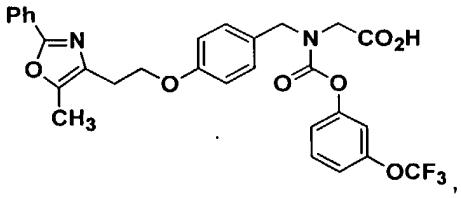

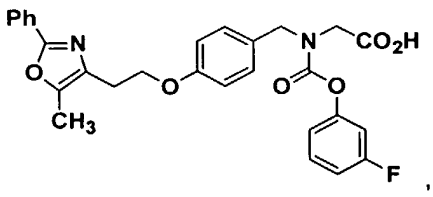

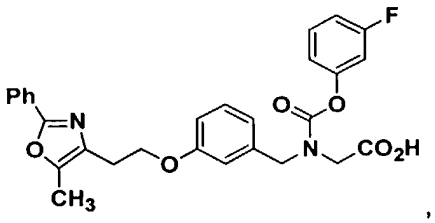

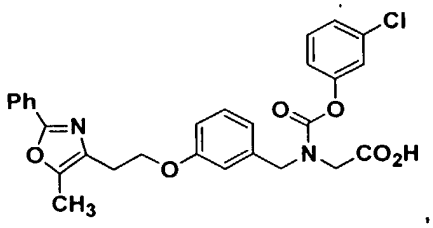

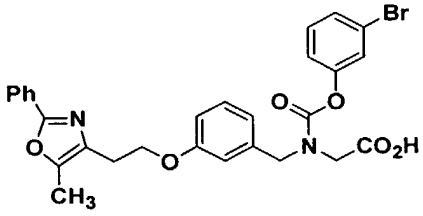

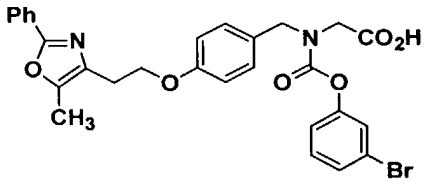

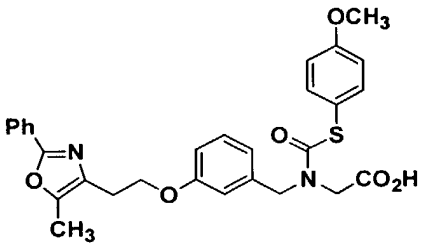

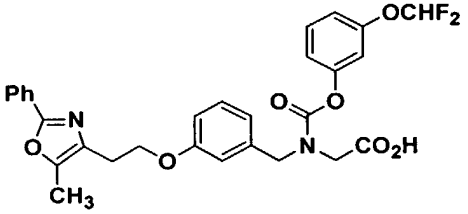

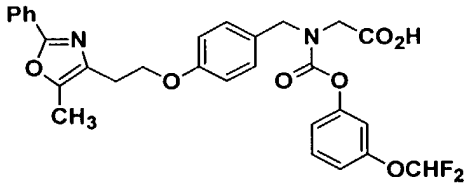

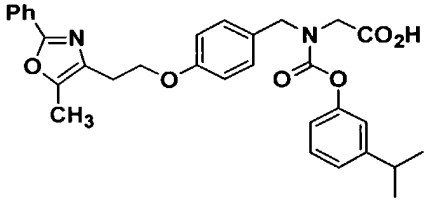

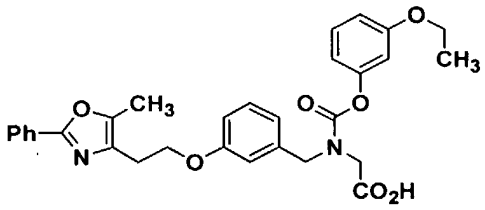

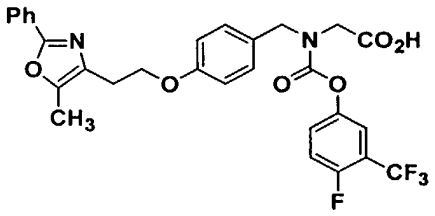

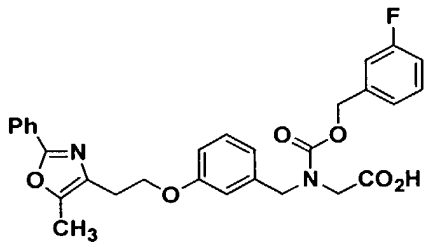

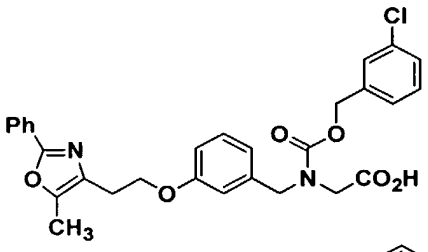

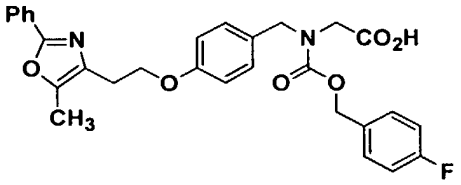

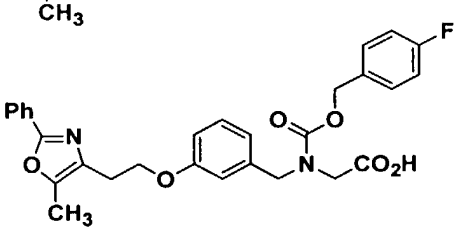

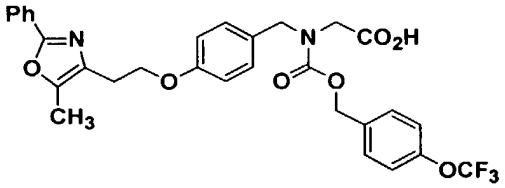

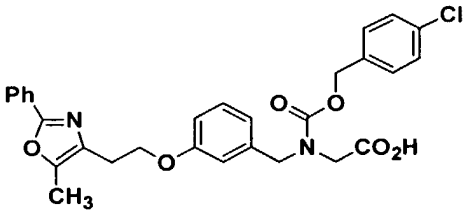

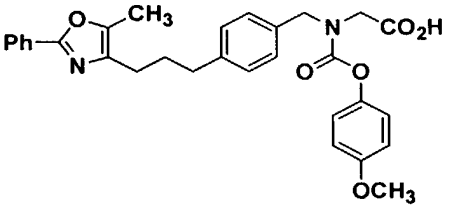

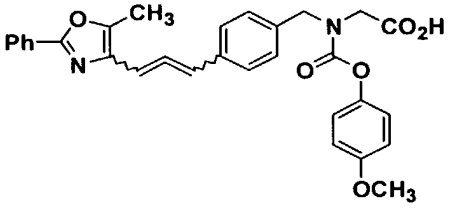

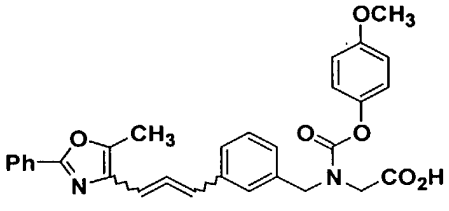

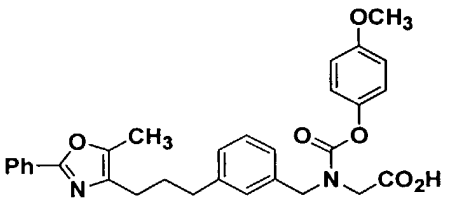

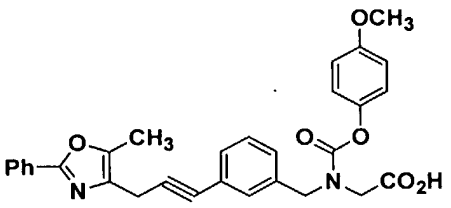

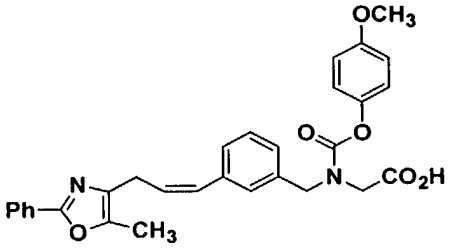

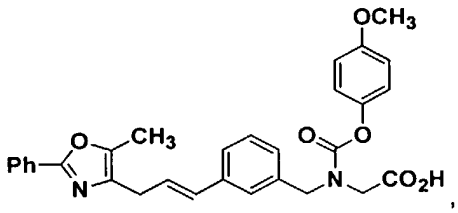

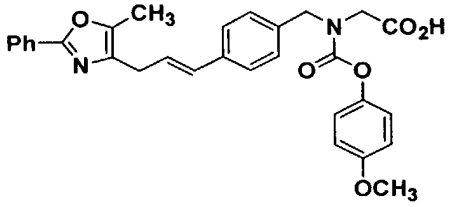

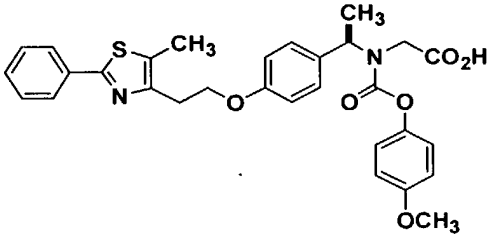

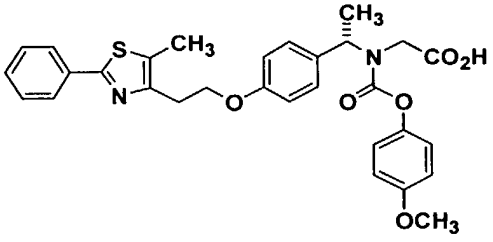

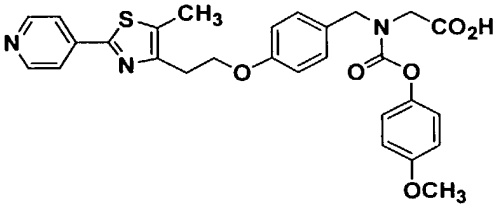

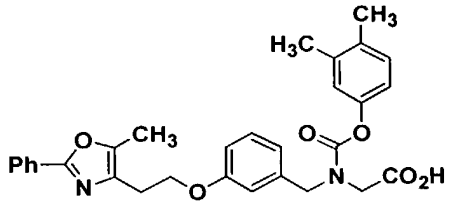

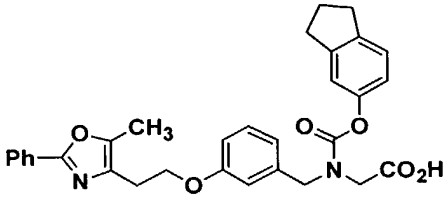

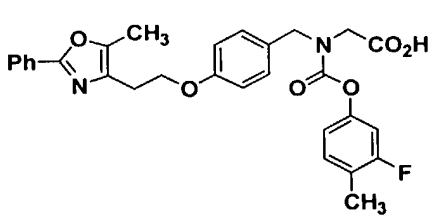

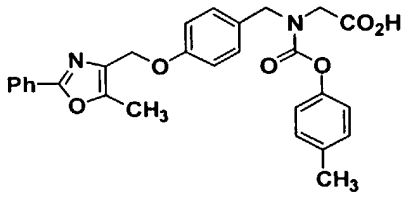

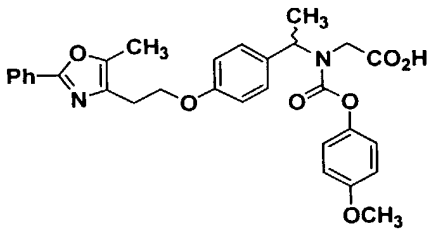

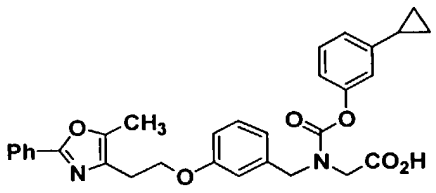

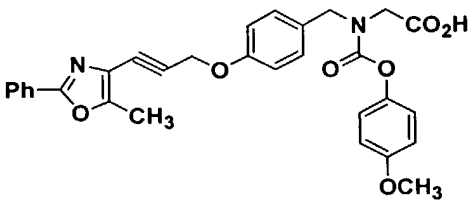

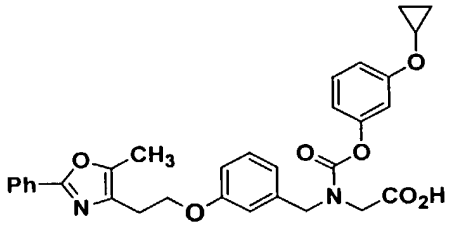

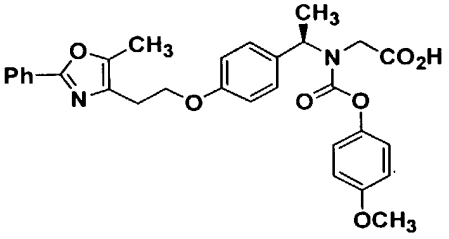

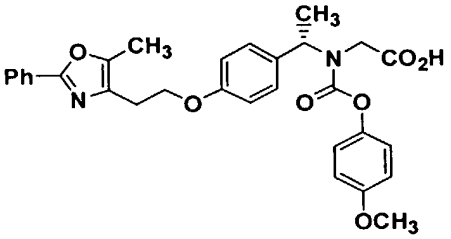

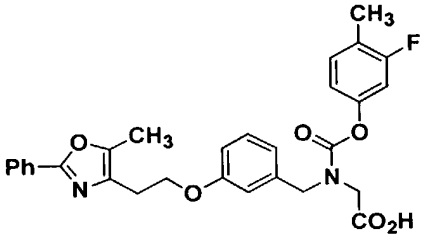

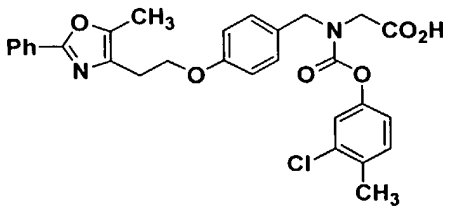

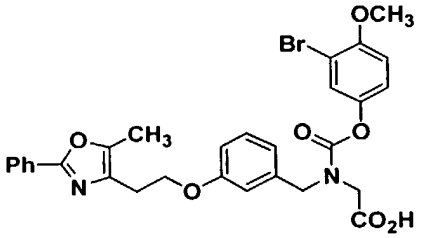

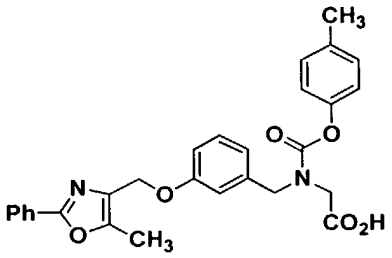

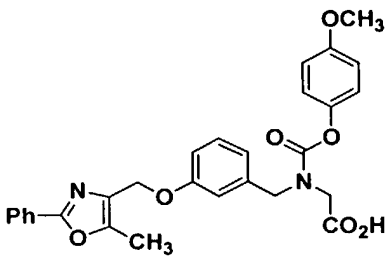

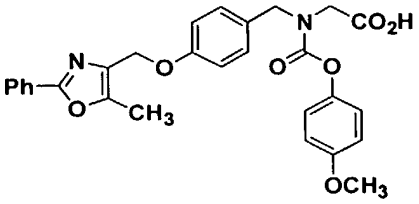

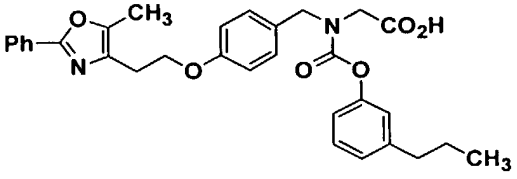

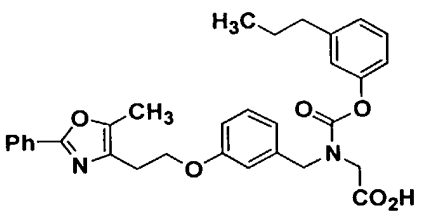

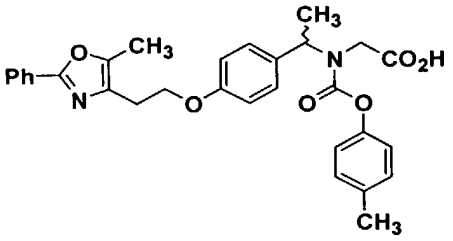

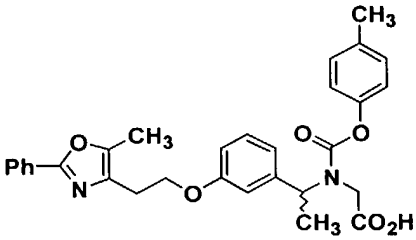

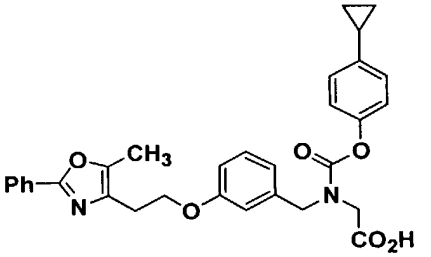

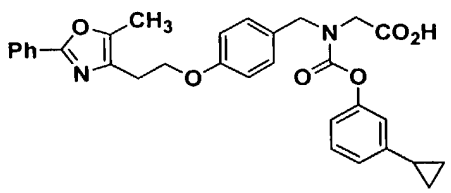

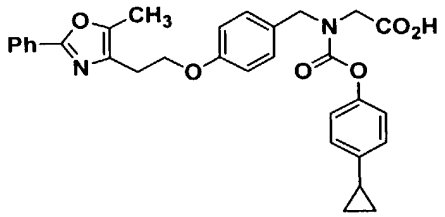

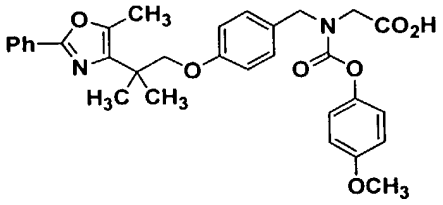

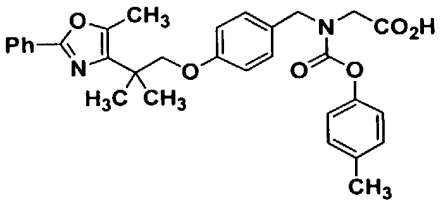

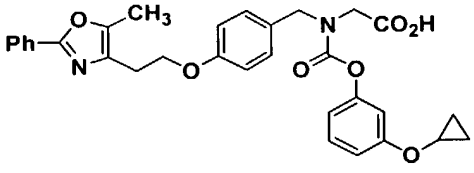

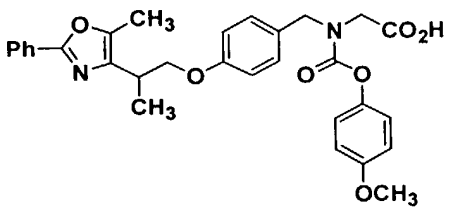

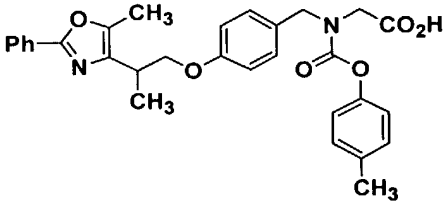

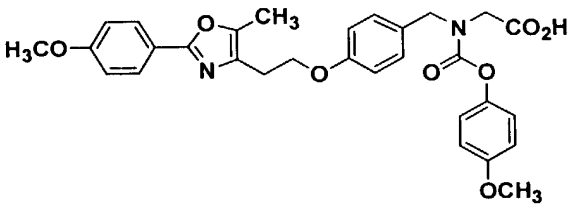

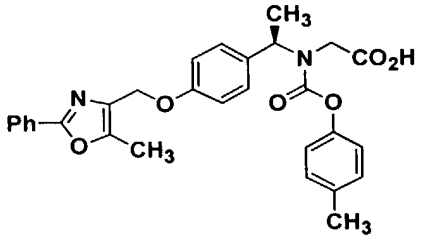

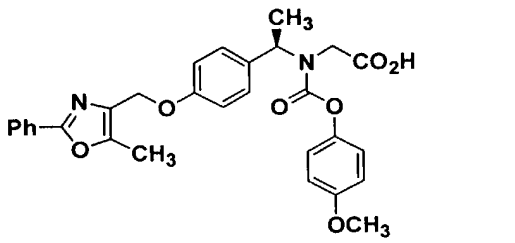

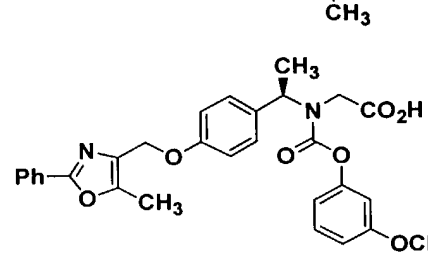

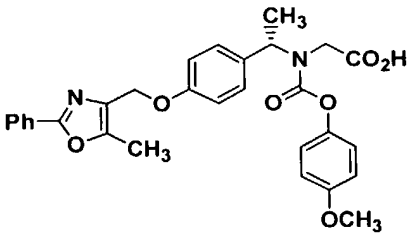

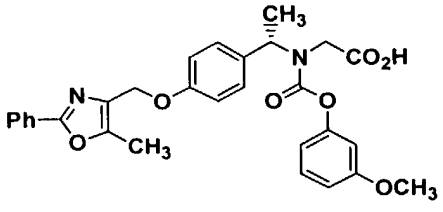

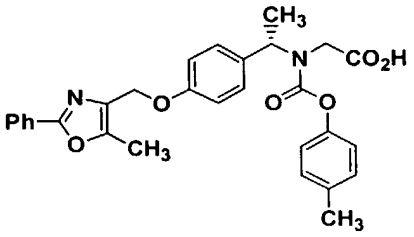

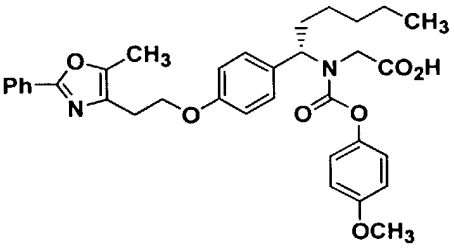

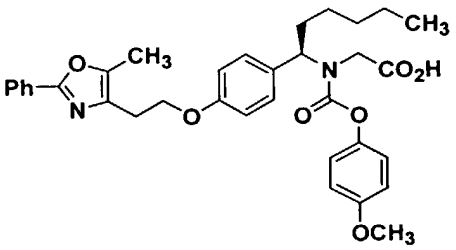

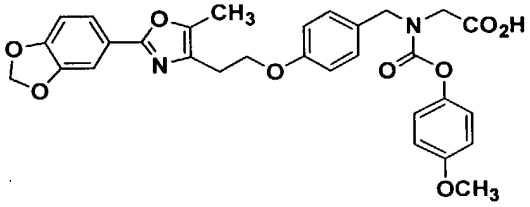

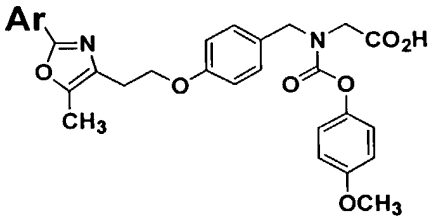

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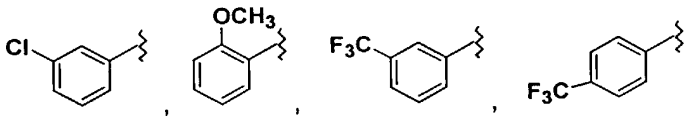
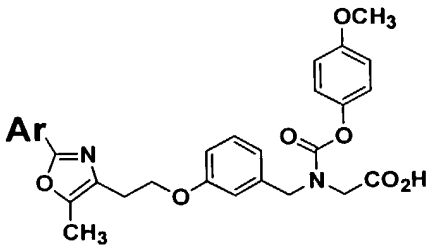
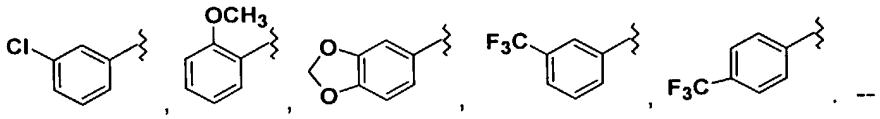
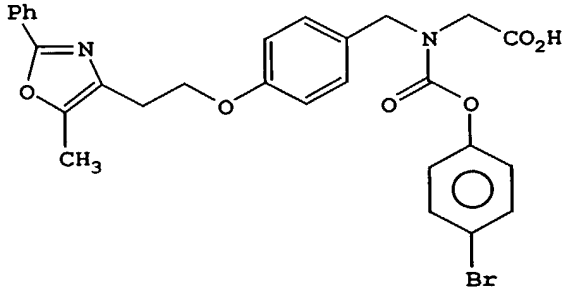


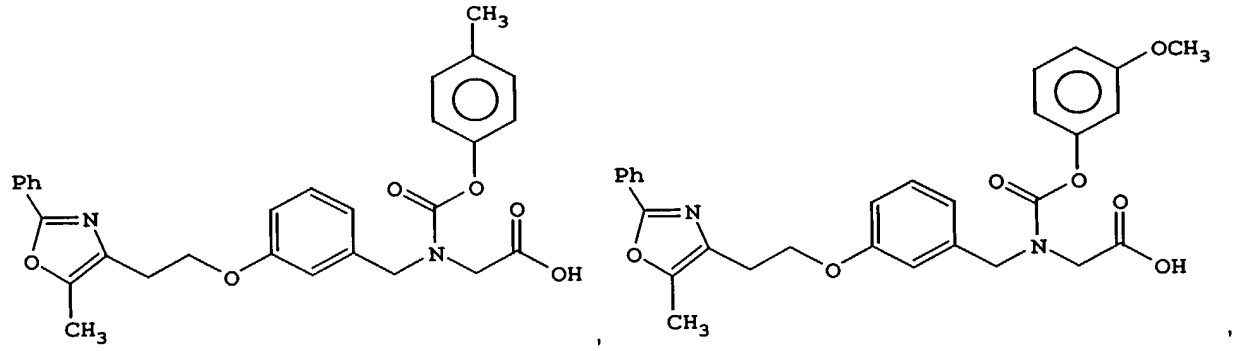


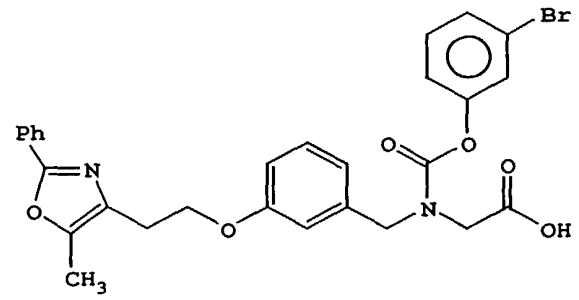
Ar = 

--21. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure

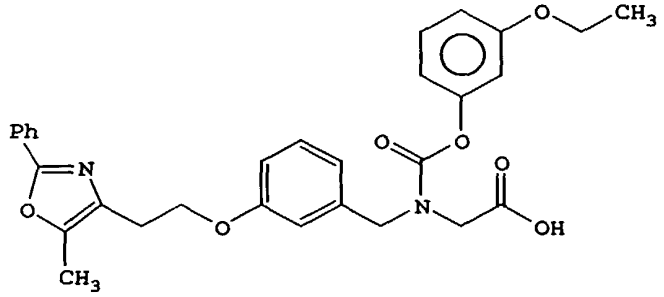


--22. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure





or



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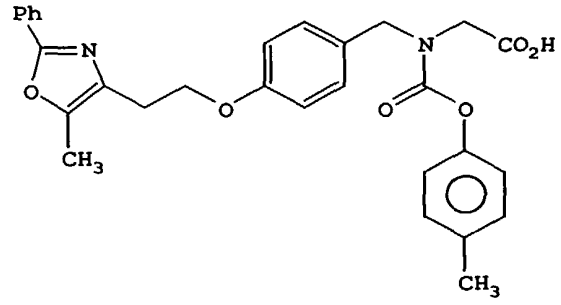
--26. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



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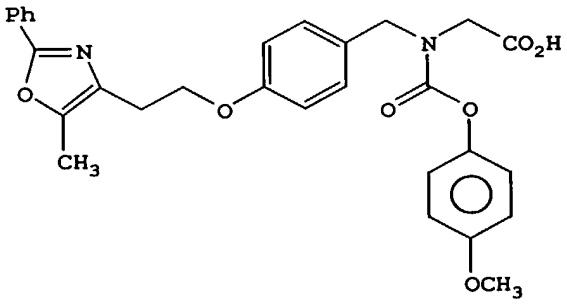
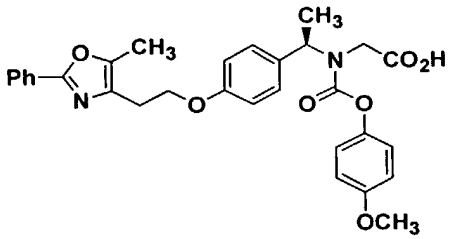
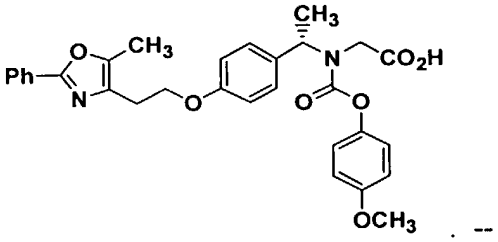
--27. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



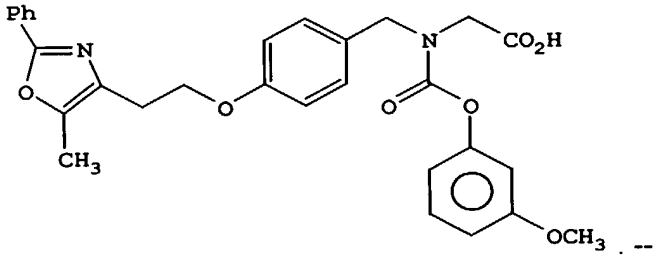
--28. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



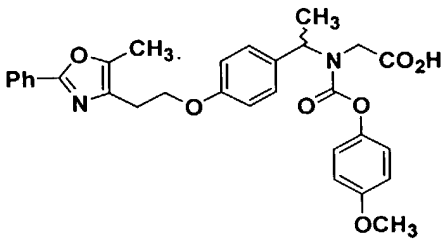
or



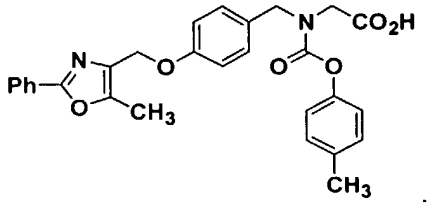
--30. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--31. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



--32. (Amended) The method as defined in Claim 55 wherein the compound employed has the structure



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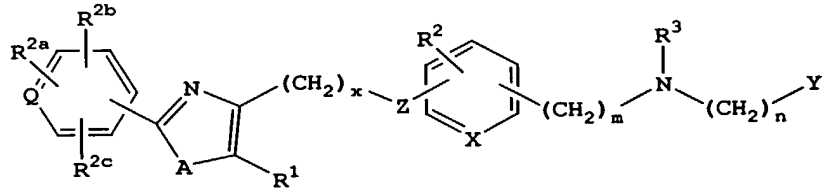
--34. (Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is CH;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

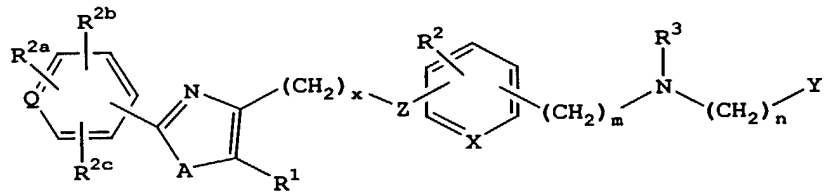
R^3 is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl,

alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO_2R^4 where R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$ where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $P(O)(OR^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--37.(Amended) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is CH;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R^3 is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl,

alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO_2R^4 where R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$ where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $P(O)(OR^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof, and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent. --

--39. (Amended) The combination as defined in Claim 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β-adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin,

itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

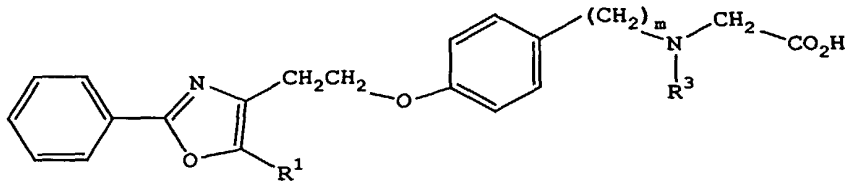
an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 37. --

Please add the following Claims 55 and 56.

55. A method for lowering blood glucose levels or for treating diabetes, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



where R^1 is alkyl,

$(CH_2)_m$ is CH_2 or $-\overset{CH_3}{\underset{|}{C}}H-$ and R^3 is aryloxycarbonyl or alkoxyaryloxycarbonyl.

56. The method as defined in Claim 55 where in the compound employed $(CH_2)_m$ is CH_2.

REMARKS

Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 34, 37, 39, 40, 50, 55 and 56 are present.

The invention in this application involves method of use claims 34, 36 and pharmaceutical combination Claim 37 and claims dependents thereon. These claims have been divided out of parent application Serial No. 09/812,960, now allowed.

The addition of R^3 as polyhaloalkylaryloxycarbonyl in Claim 1 is based on original Claim 10, lines 29-30.

Claims 34 to 37 have been combined.

Claims 39, 42, 44 and 47 have been combined.

Claims 40, 43, 45, 48 and 49 have been combined.

Claims 50 and 51 have been combined.

The compounds claimed in the method of use and pharmaceutical combination claims are those which have been allowed in parent application Serial No. 09/812,960. Accordingly, it is submitted that the methods of use and combinations claimed herein which include the compounds allowed in parent application Serial No. 09/812,960 are patentable as well.

Accordingly., it is submitted that Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 31, 32, 34, and 36 to 56 are patentable for the same reasons that the compounds of parent application Serial No. 09/812, 960 have been deemed patentable. Thus, it is believed that the above claims are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

Date: 2/22/02

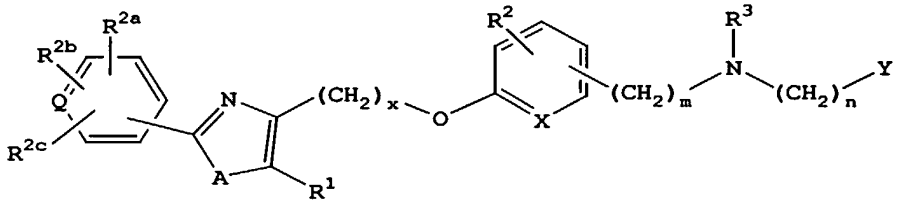
Burton Rodney
Attorney for Applicants
Reg. No. 22,076

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please cancel Claims 1, 6 to 9, 11 to 13, 15, 19, 23 to 25, 29, 33 and 35.

Please amend Claims 2 to 5, 10, 14, 16 to 18, 20 to 22, 26 to 28, 30 to 32, 34, 36 and 37 as follows.

--2. (Amended) The method as defined in Claim 34 wherein the [A] compound [having] employed has the structure



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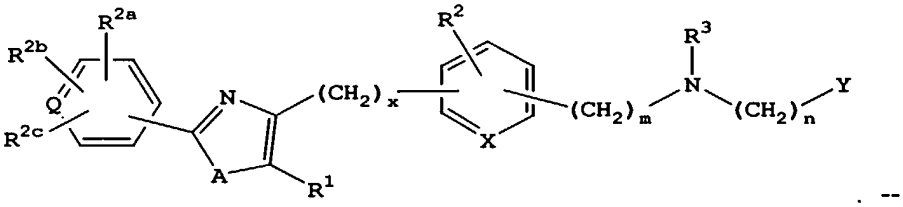

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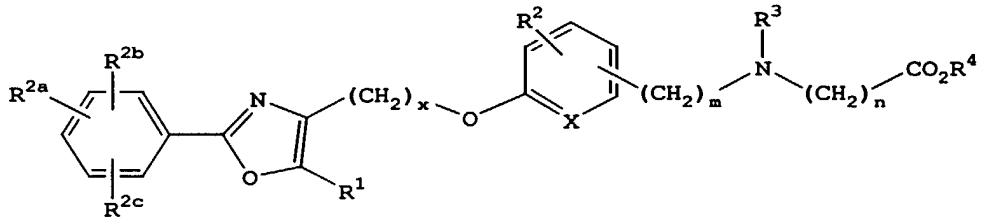
--3. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



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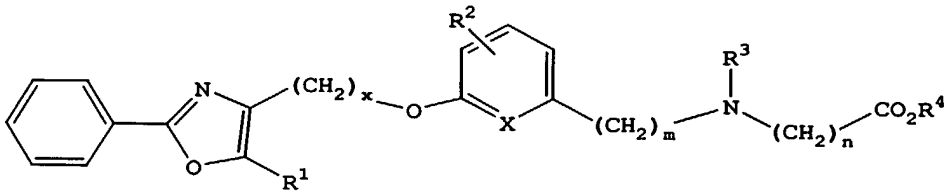
--4. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



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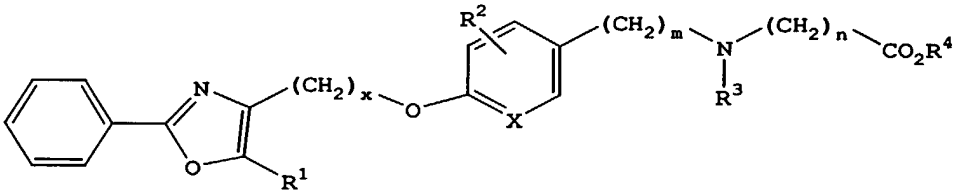
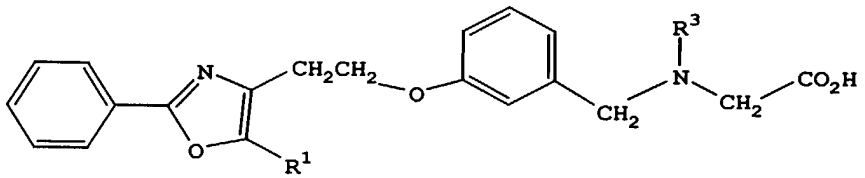


--5. (Amended) The [compound] method as defined in Claim [1] 34 where in the compound employed [wherein] $(CH_2)x$ is alkylene, alkenylene, allenyl, or alkynylene. --

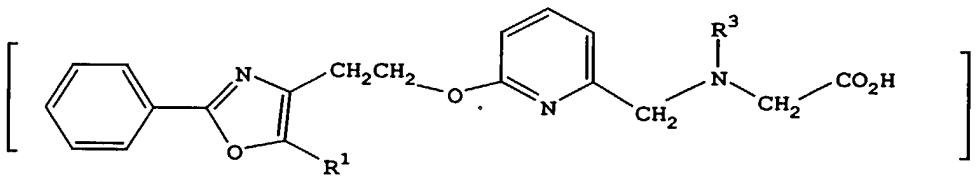
--10. (Amended) The [compound] method as defined in Claim [1] 34 [wherein R^{2a} is alkoxy or H,] where in the compound employed

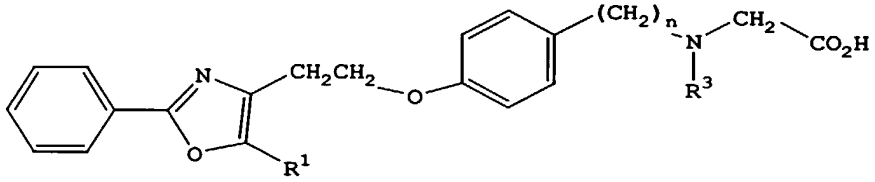
$(CH_2)_x$ is CH_2, $(CH_2)_2$, $(CH_2)_3$, or $-\overset{CH_3}{\underset{CH_3}{C}}-$, $(CH_2)_m$ is CH_2, or $-\overset{R_a}{CH}-$ [(]where R_a is alkyl or alkenyl[)], $(CH_2)_n$ is CH_2, R^1 is lower alkyl, [preferably $-CH_3$,] R^2 is H, R^{2a} is H, R^4 is H, [X is CH,] and R^3 is arylalkyloxycarbonyl, [arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl,] aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, [aryloxyarylcarbonyl,] arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, [arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl,] cycloalkyloxyaryloxycarbonyl, [heteroaryl-heteroarylcarbonyl,] alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, [alkoxyarylalkyl,] arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted.--

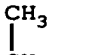
--14. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has the [having the] structure



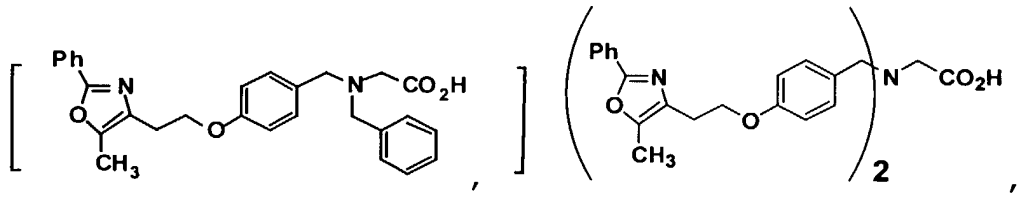
or

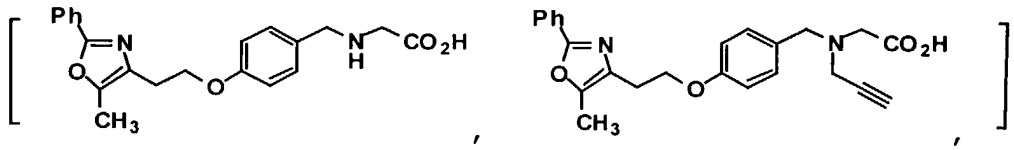


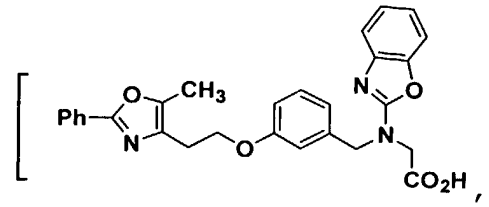


where $(CH_2)_n$ is CH_2 or  . --

--16. (Amended) The [compound] method as defined in Claim [1 having] 34 wherein the compound employed has the structure







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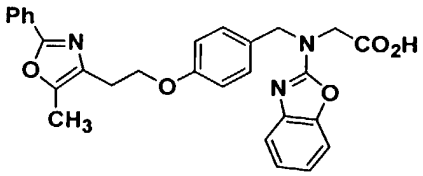

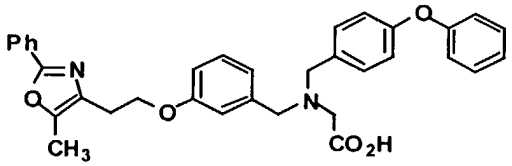

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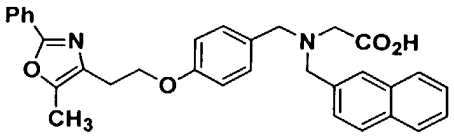

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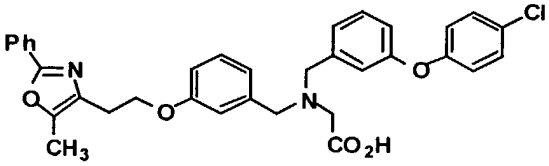

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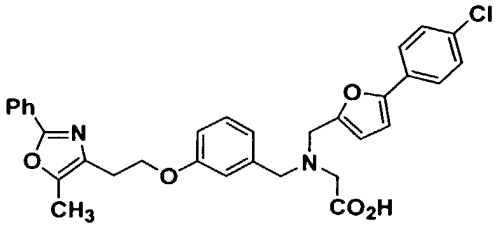

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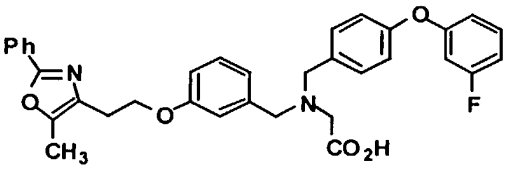

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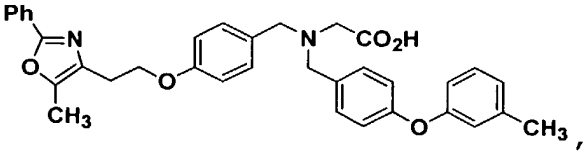

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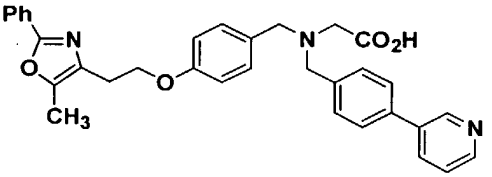

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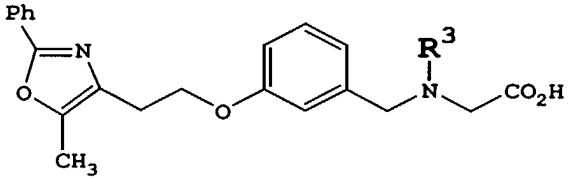

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where R^3 =

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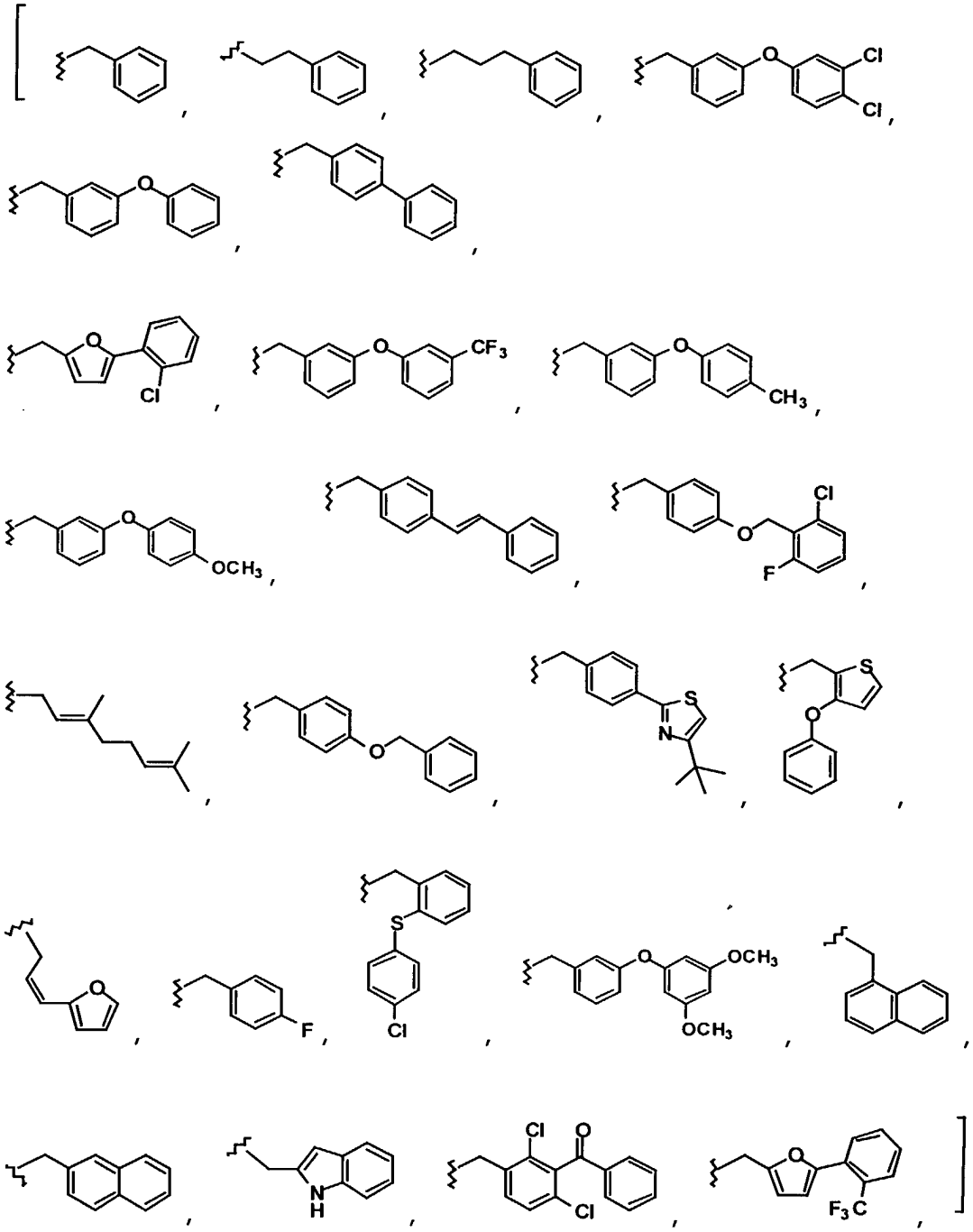

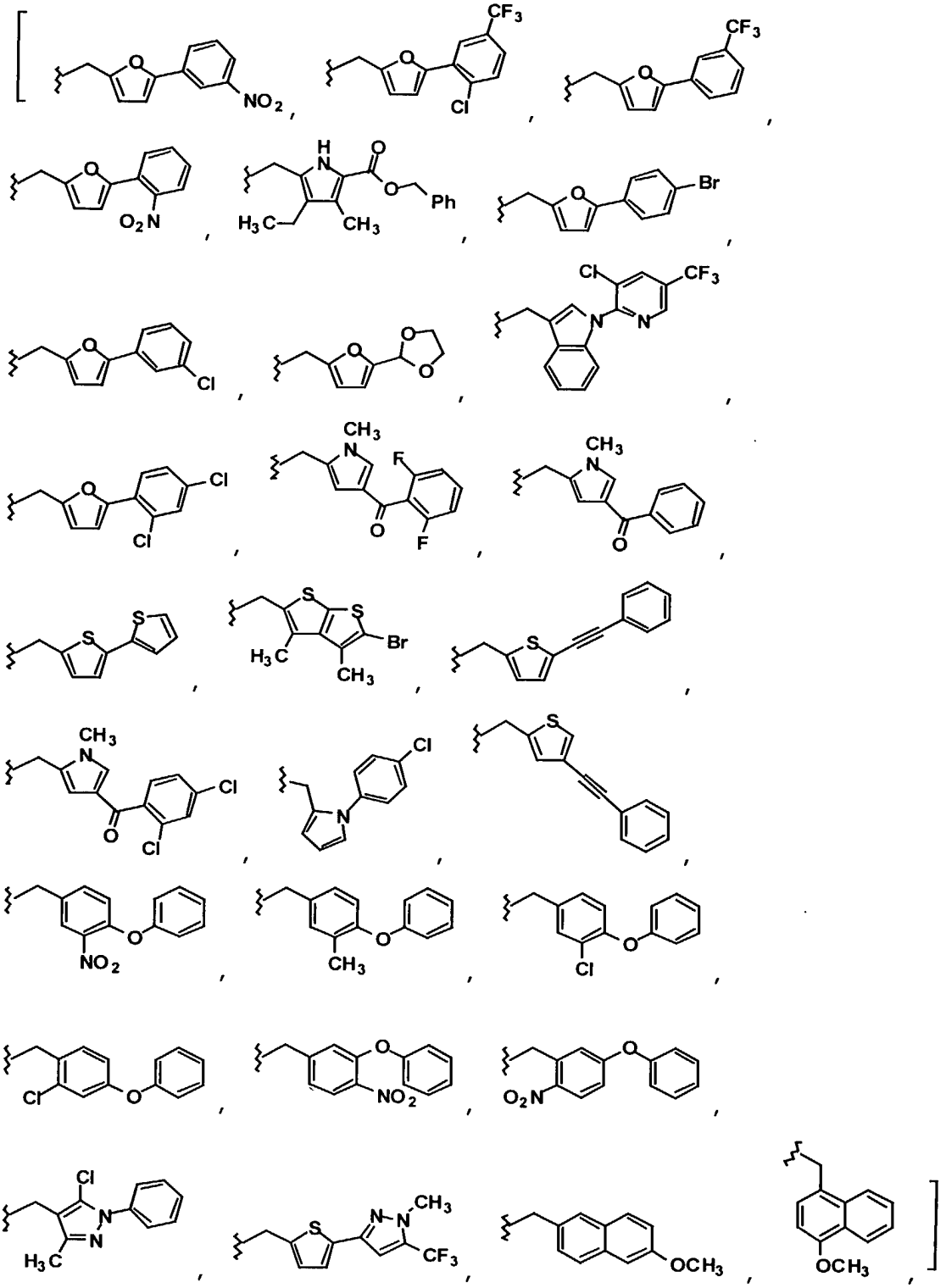

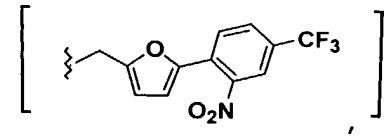

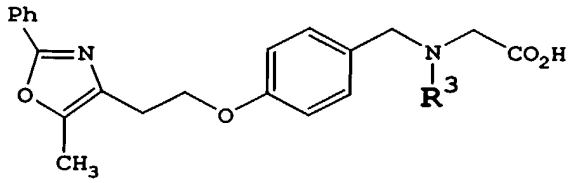

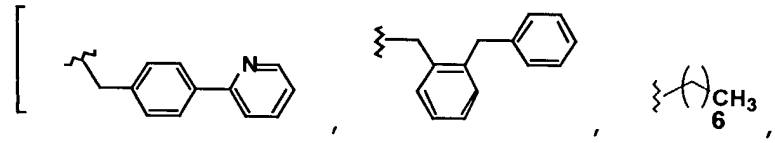

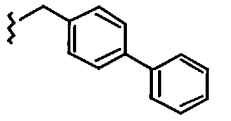

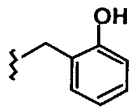

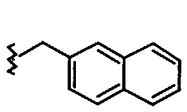

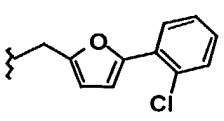

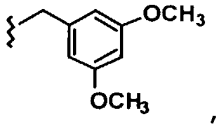

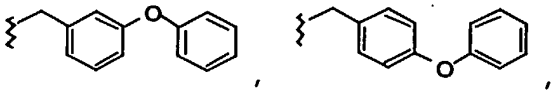

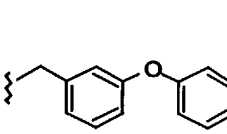

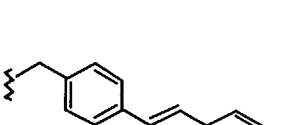

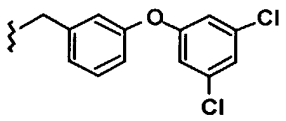

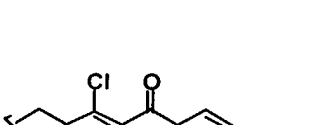

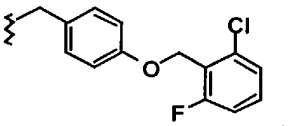

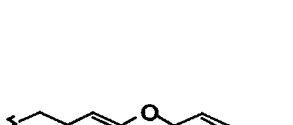

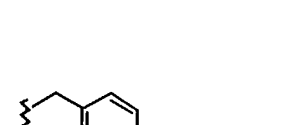

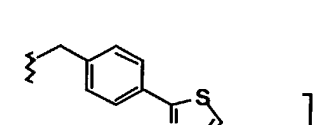

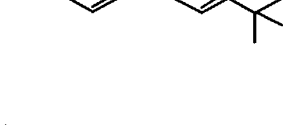

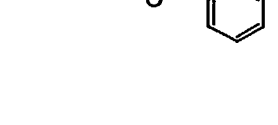

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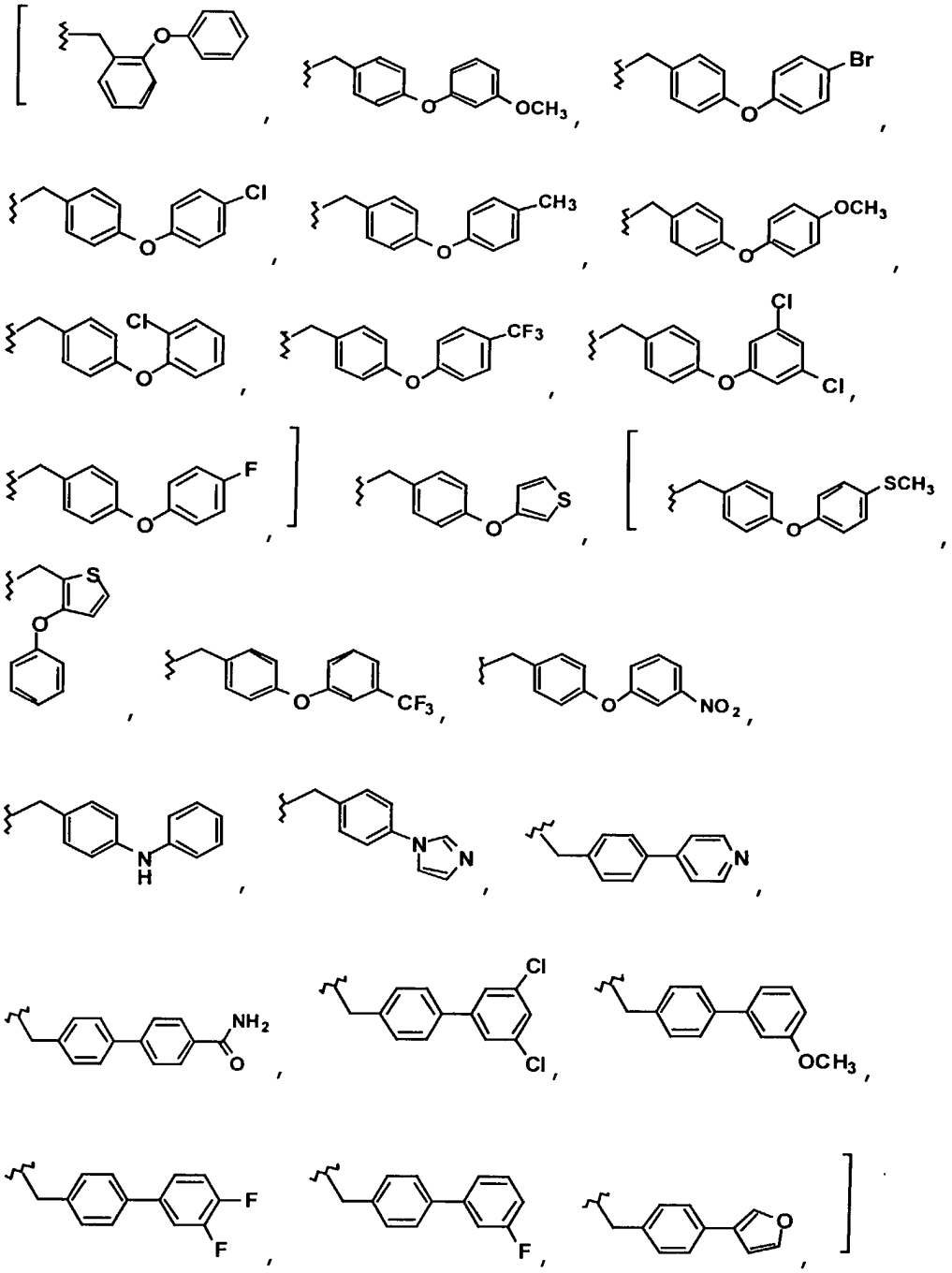

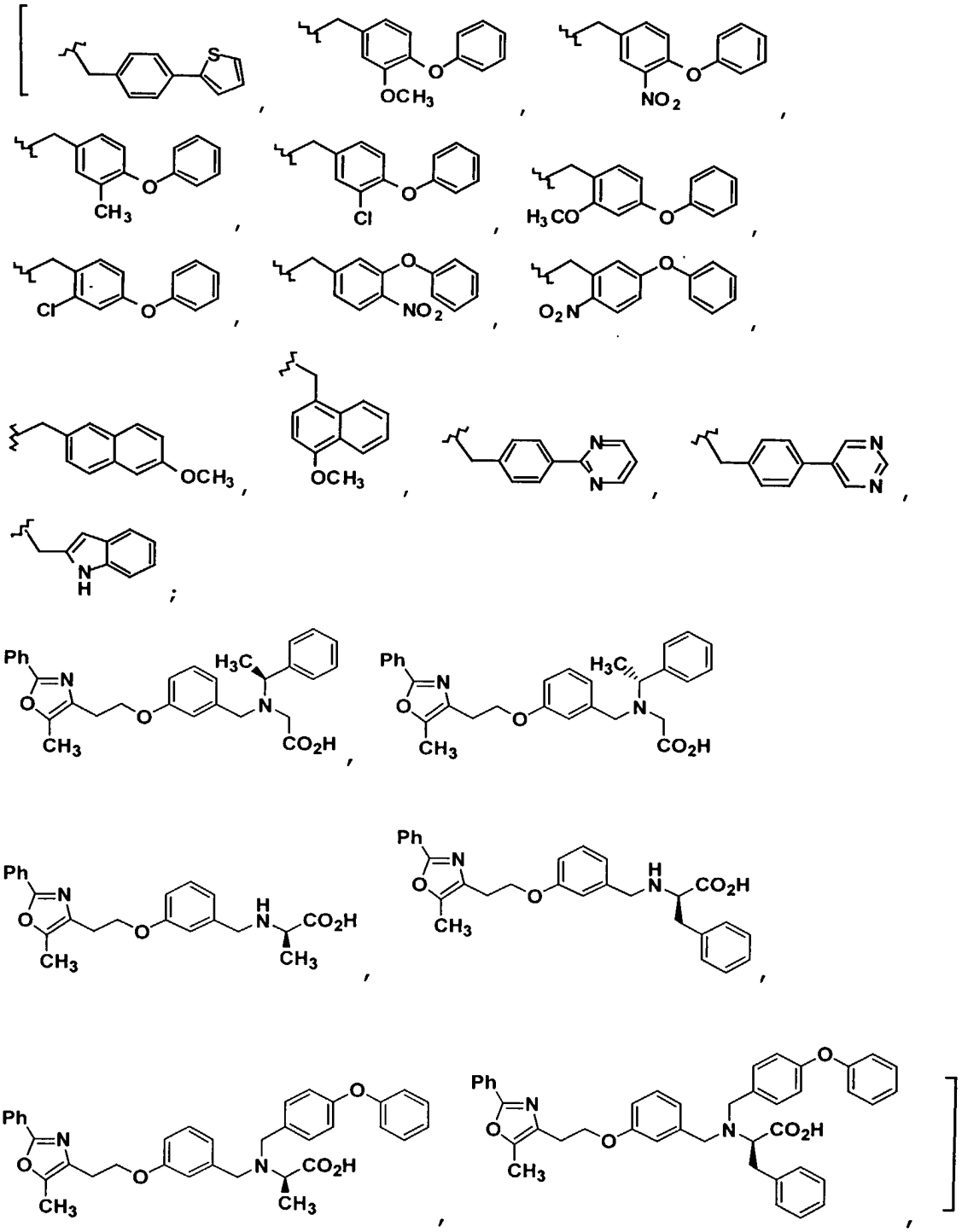

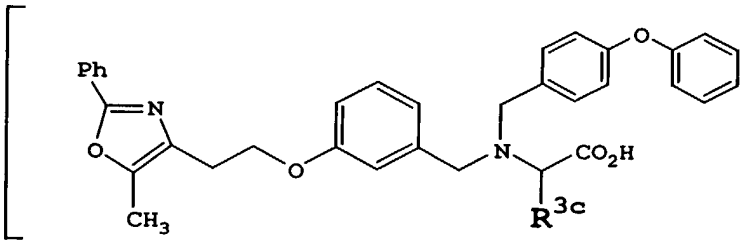

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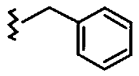
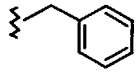
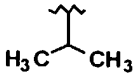
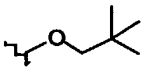
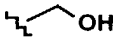
[(S)-CH_3,  , (R)-CH_3,  ,  ,  , ]

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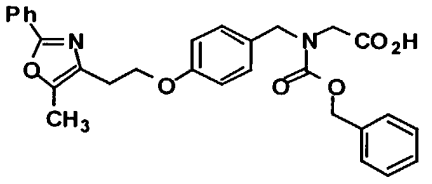
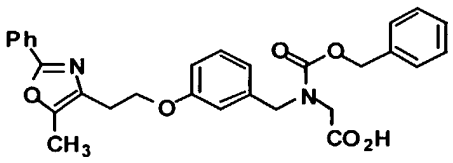
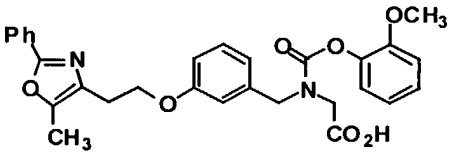
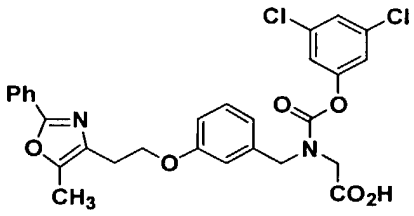
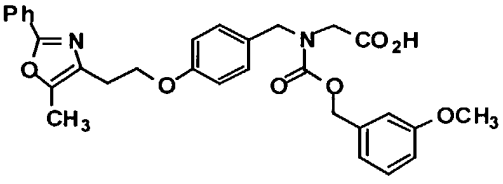
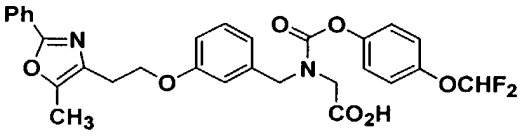
 ,

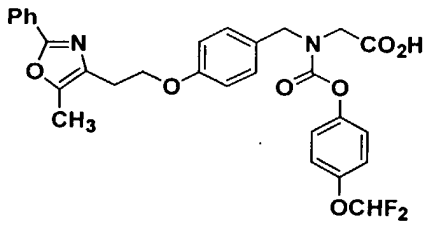
 ,

 ,

 ,

 ,

 ,



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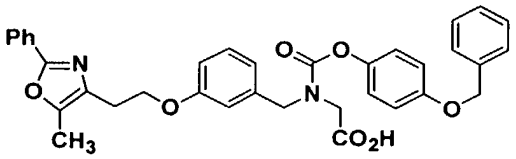

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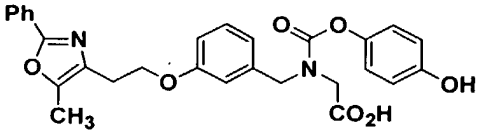

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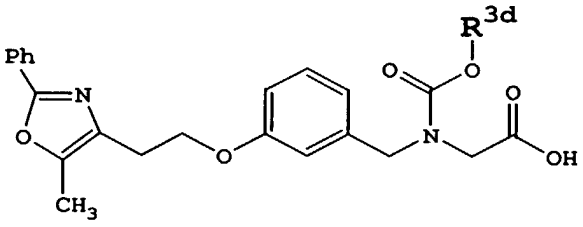

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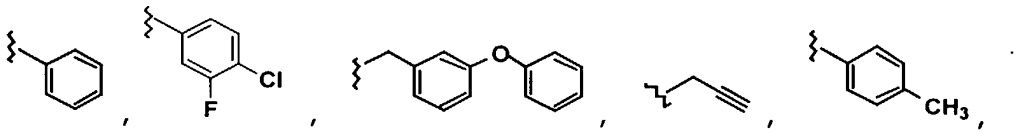

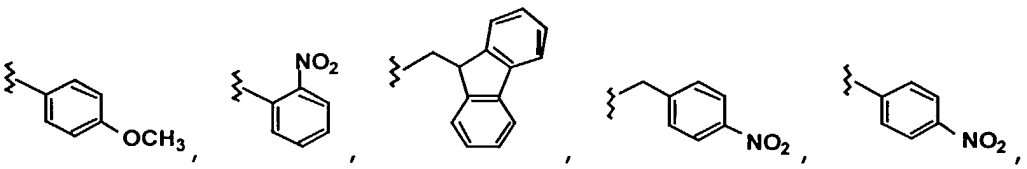

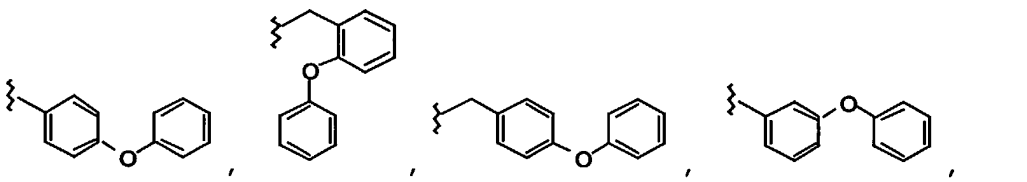

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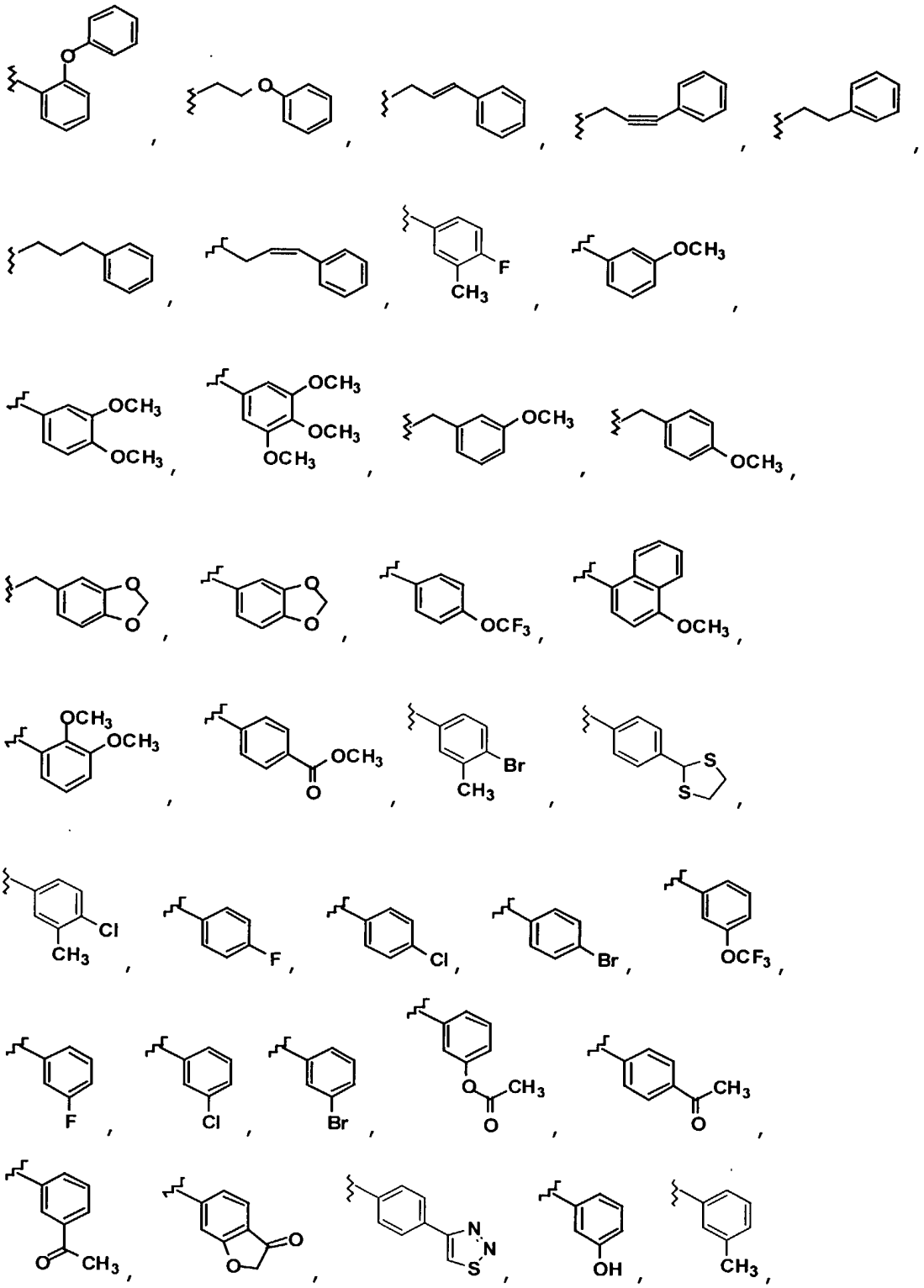

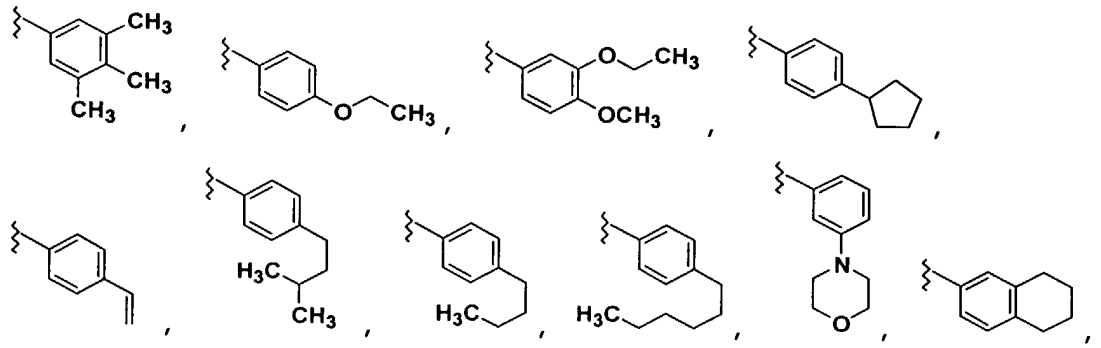

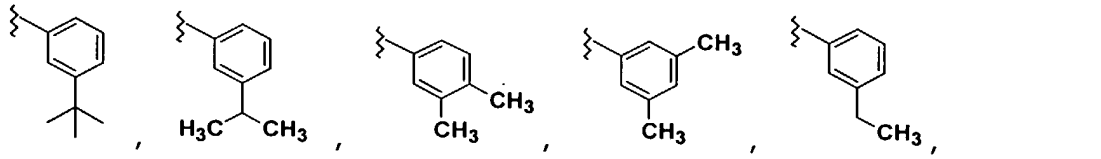

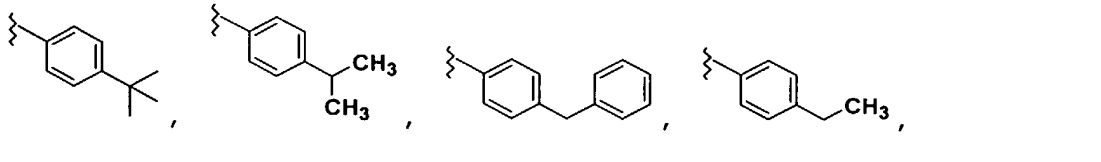

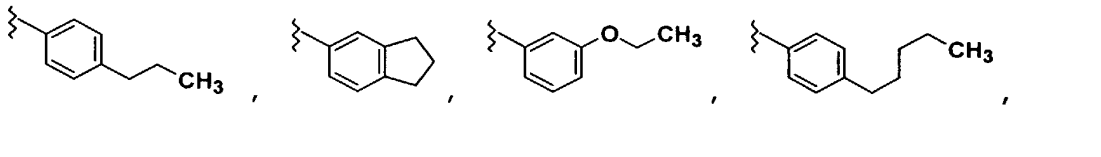

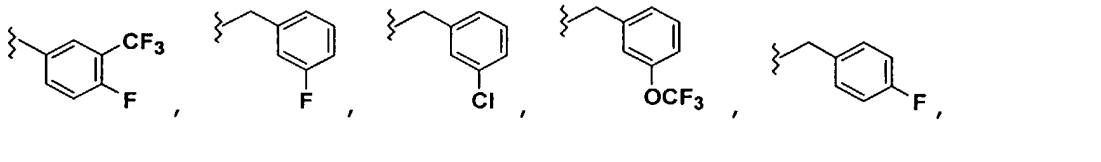

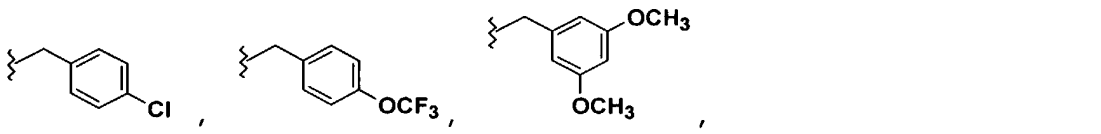

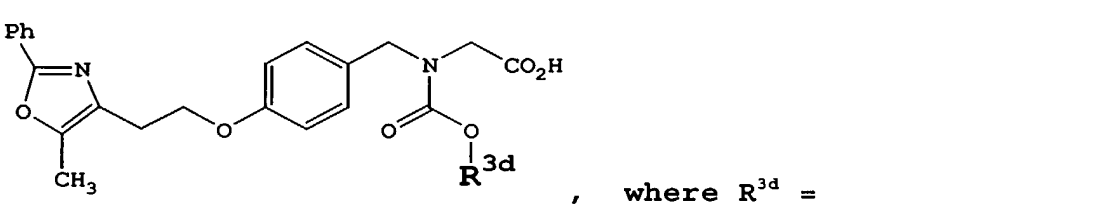

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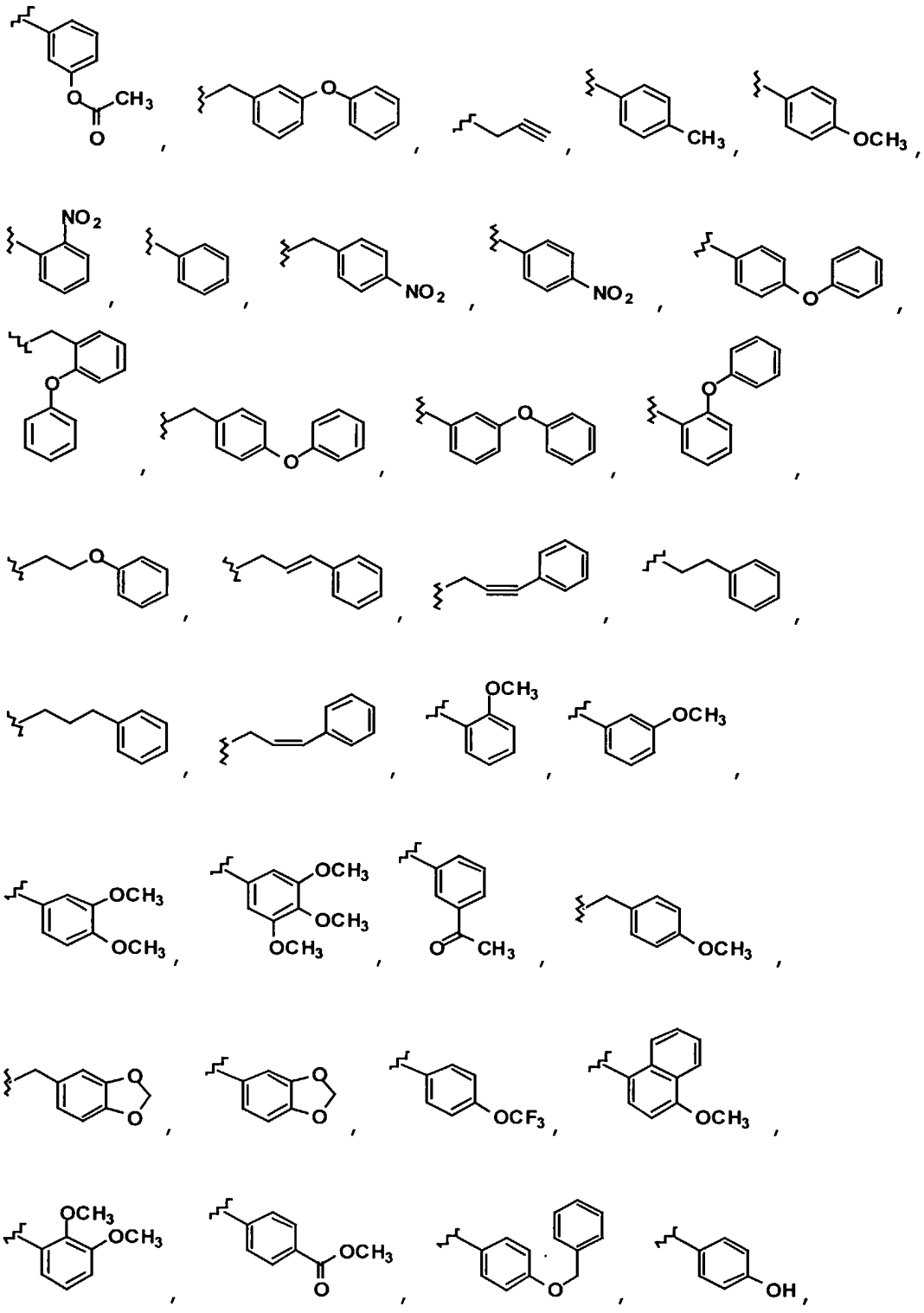

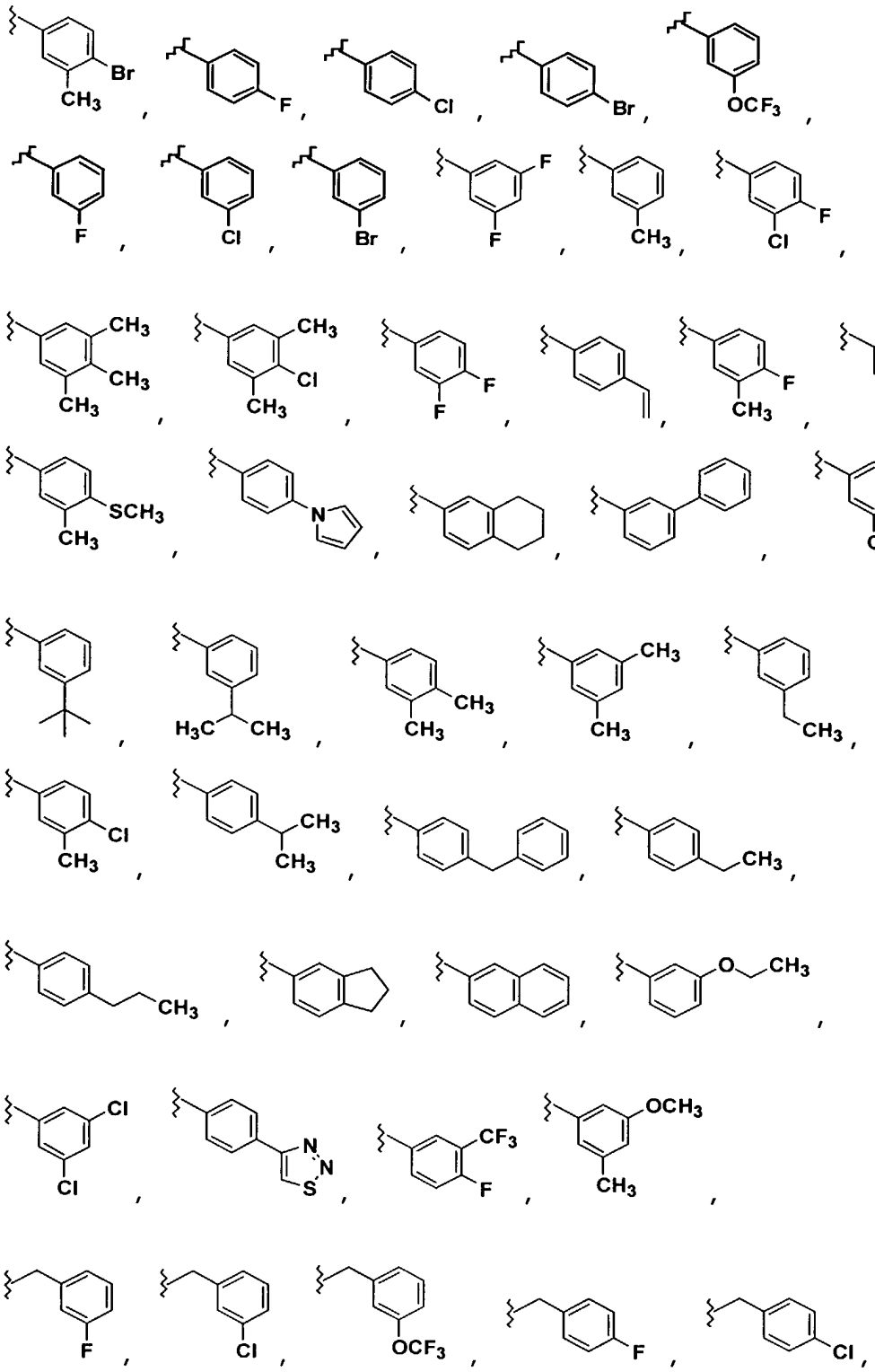

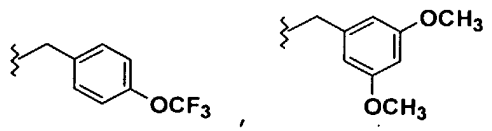

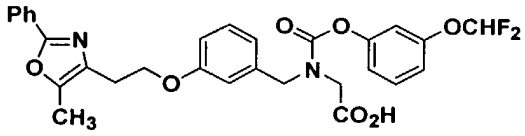
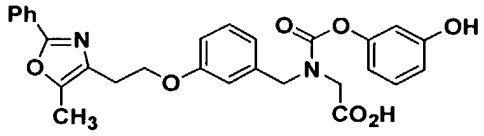

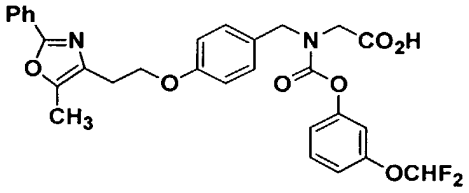
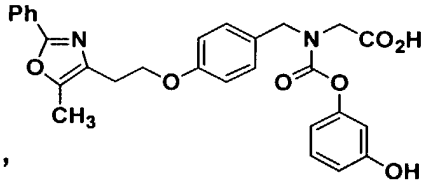

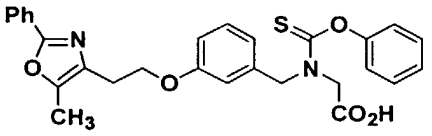
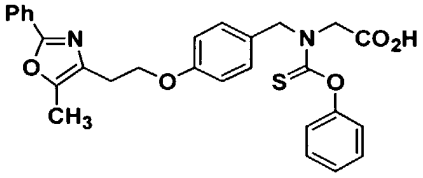

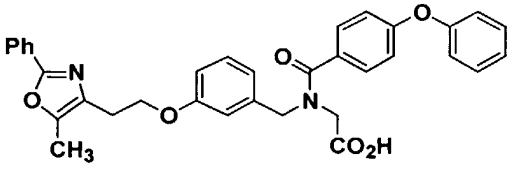
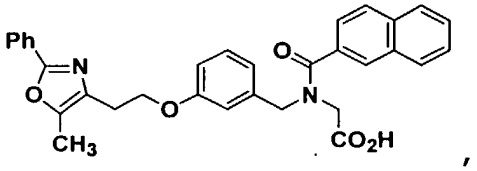

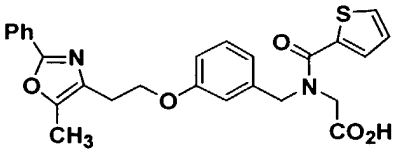
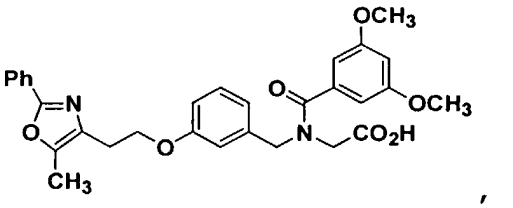

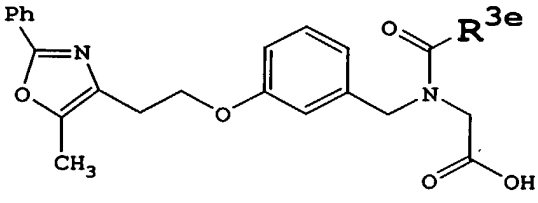
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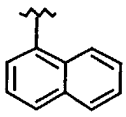
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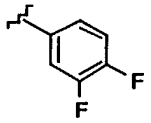
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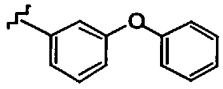
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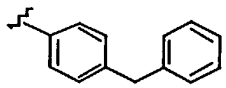
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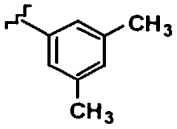
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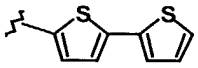
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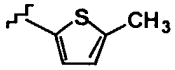
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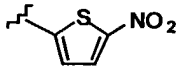
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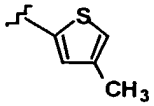
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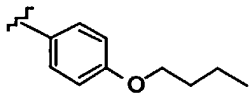
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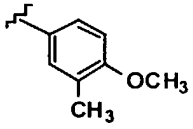
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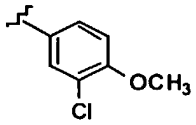
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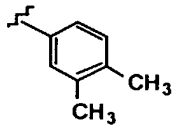
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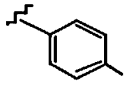
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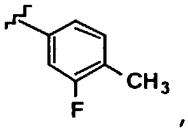
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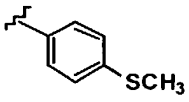
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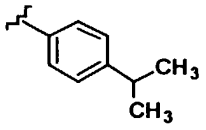
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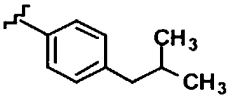
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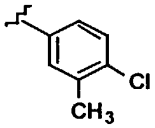
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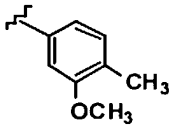
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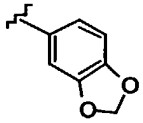
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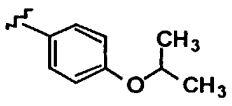
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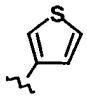
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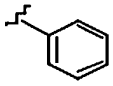
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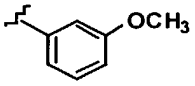
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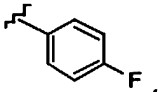
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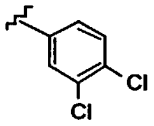
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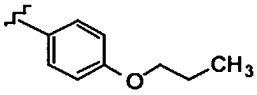
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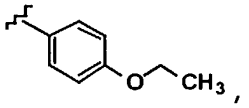
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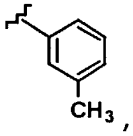
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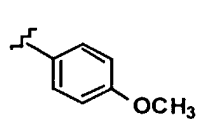

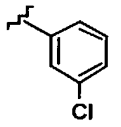

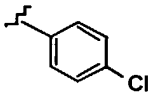

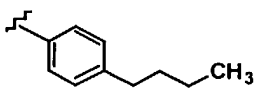

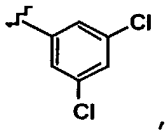

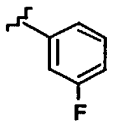

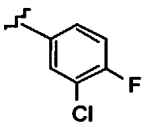

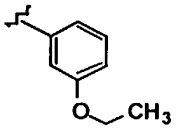

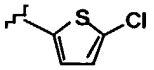

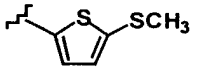

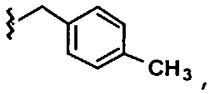

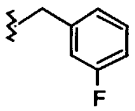

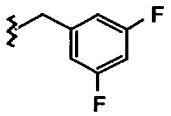

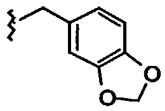

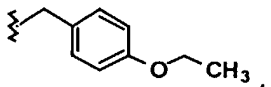

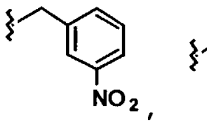

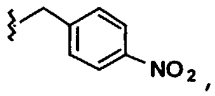

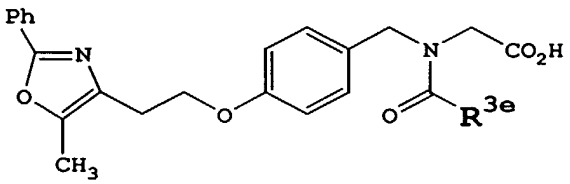

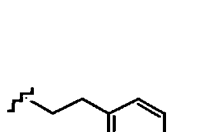

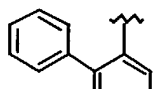

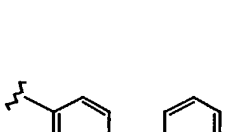

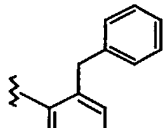

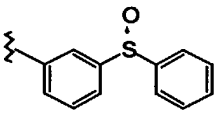

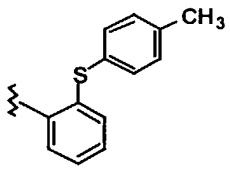

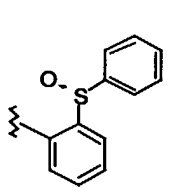

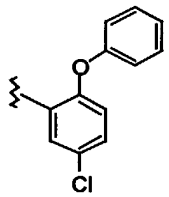

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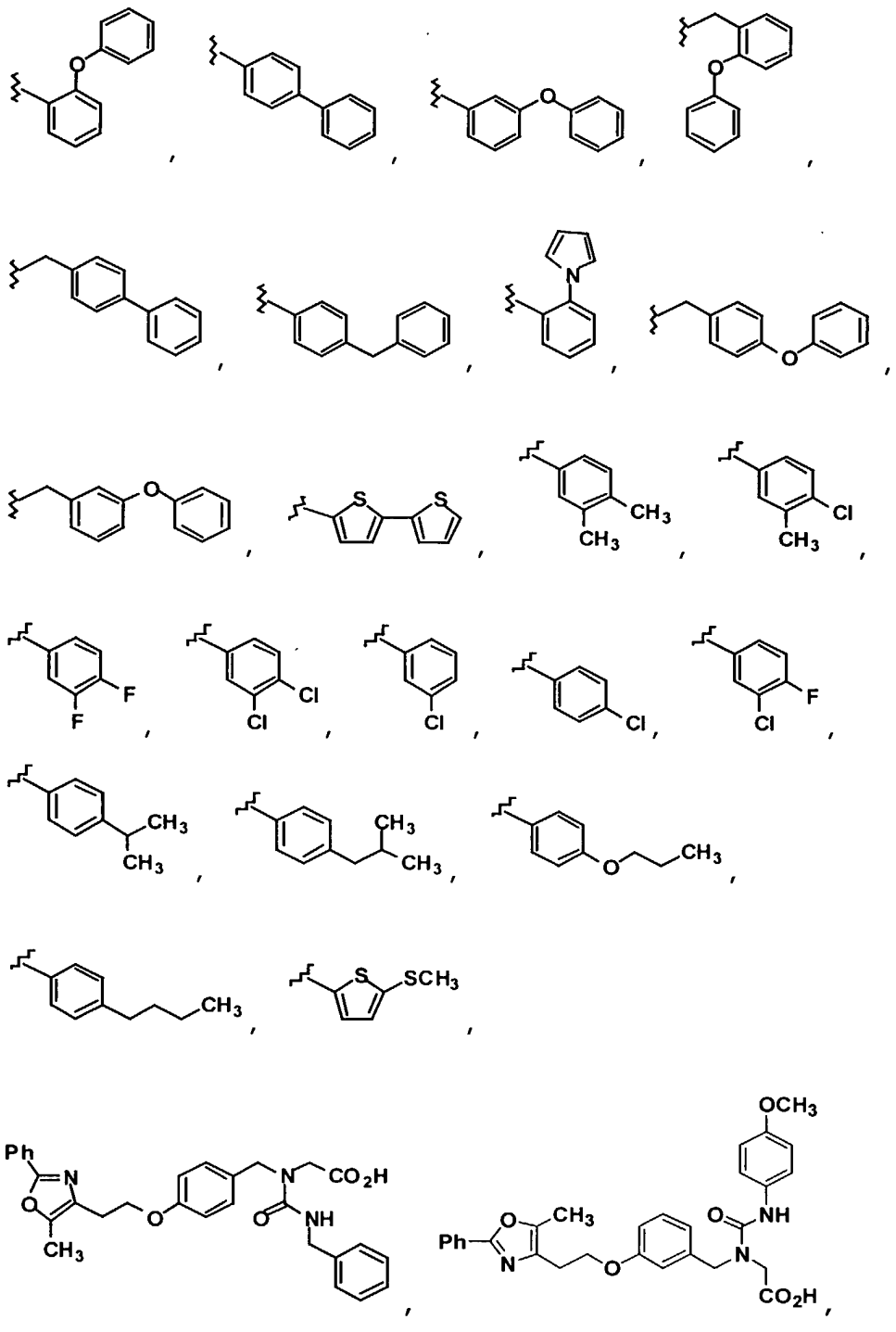
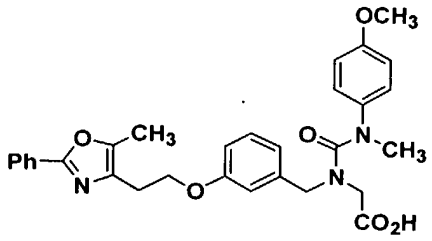
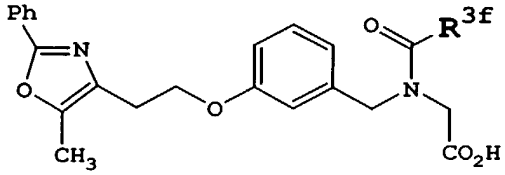
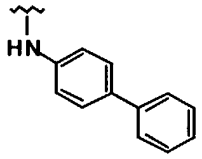
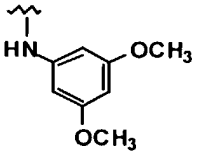
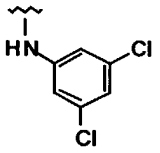
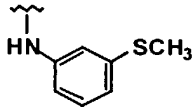
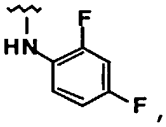
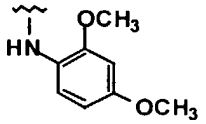
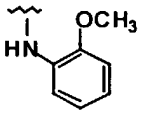
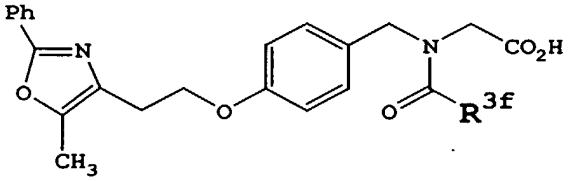




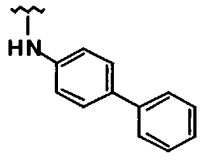
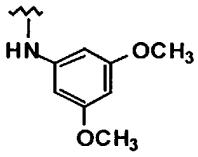
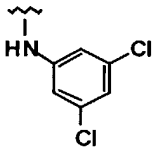
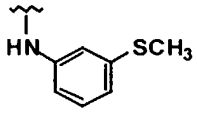
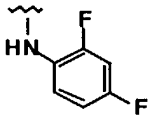
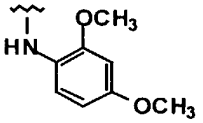
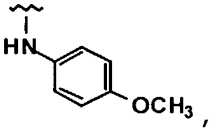
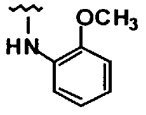


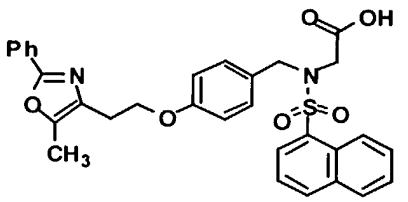
where R^{3f} =

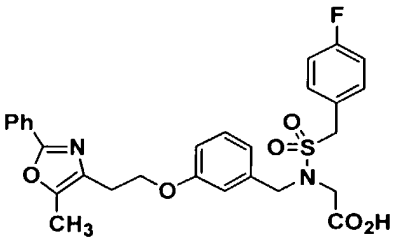








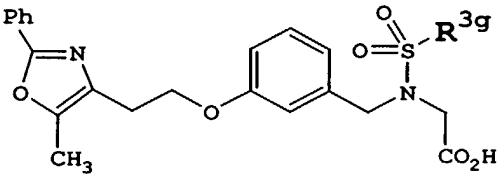


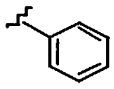
where R^{3f} =

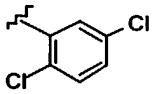









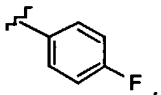


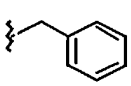


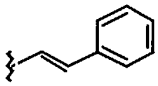


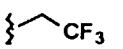


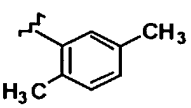


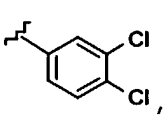


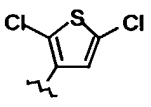


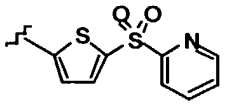


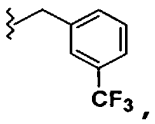


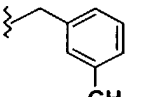


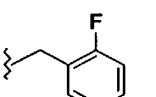


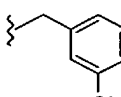


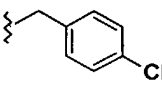


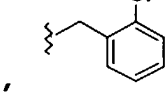


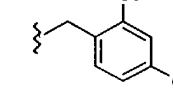


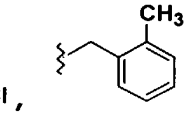


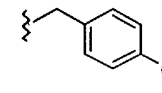


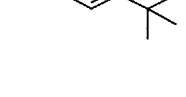












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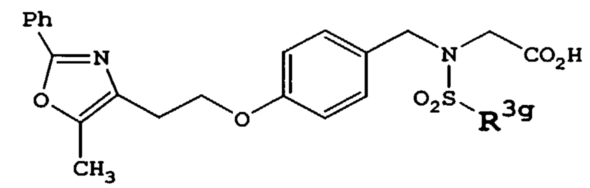

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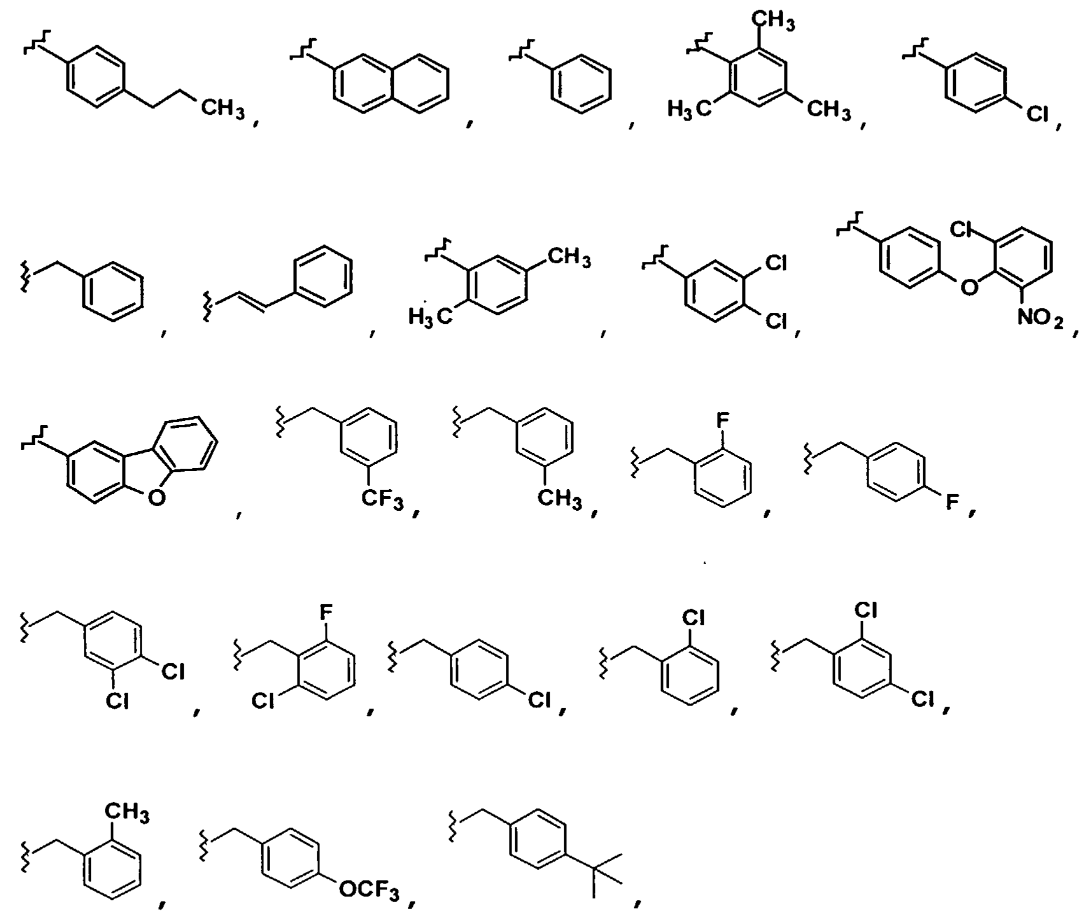

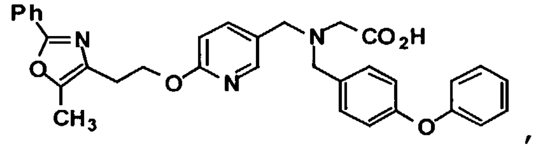

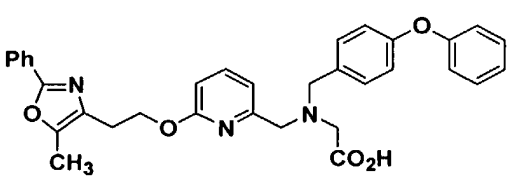
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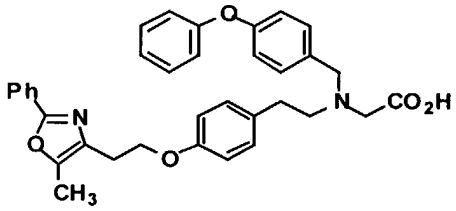
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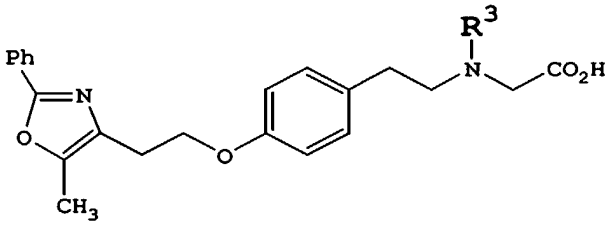
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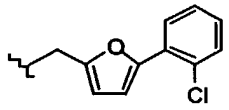
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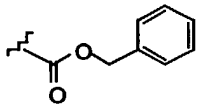
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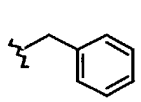
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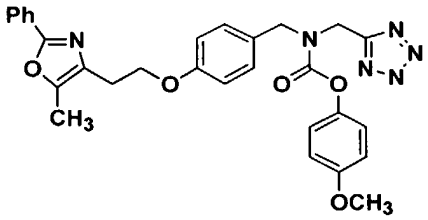
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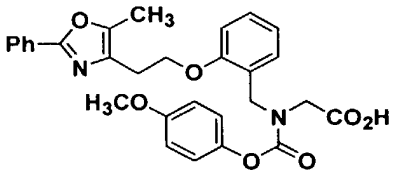
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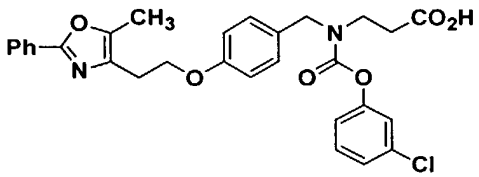
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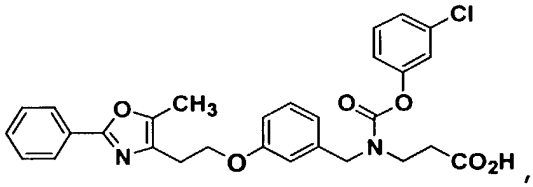
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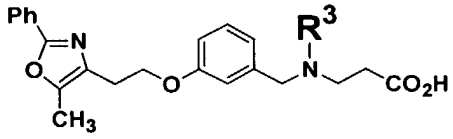
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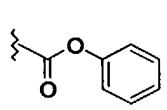
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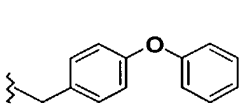
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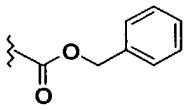
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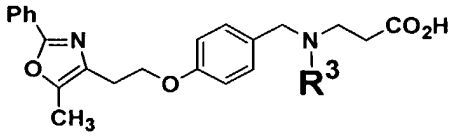

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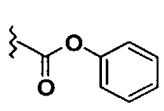
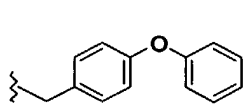
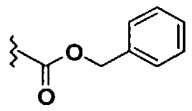
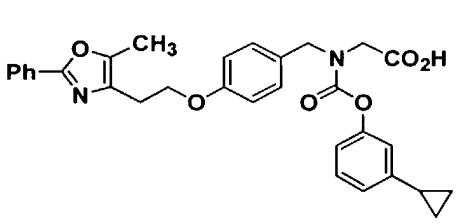
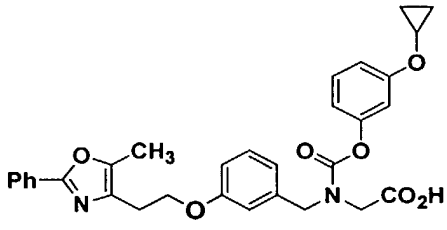
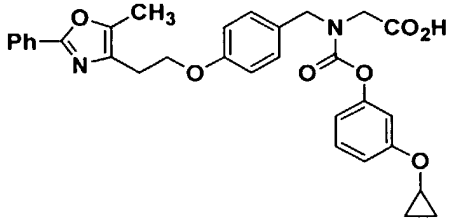
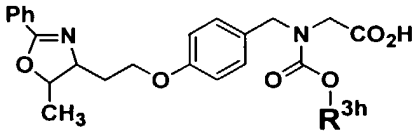
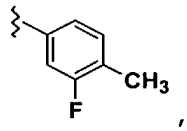
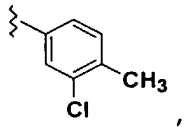
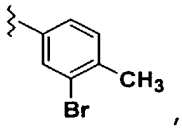




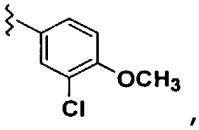



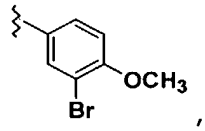
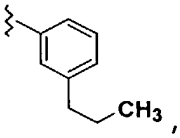
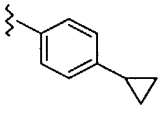
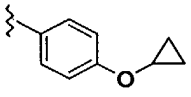


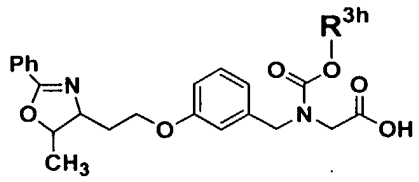


, where R^{3h} =





, where R^{3h} =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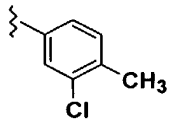
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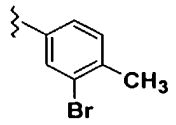
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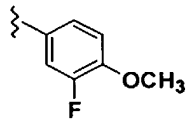
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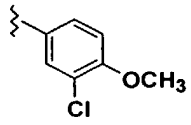
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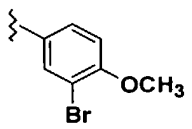
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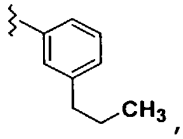
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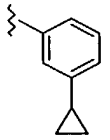
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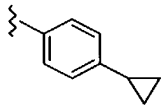
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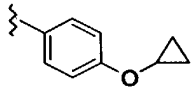
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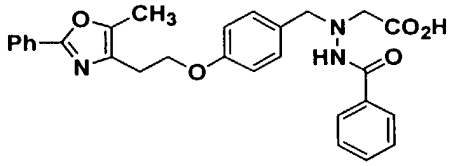
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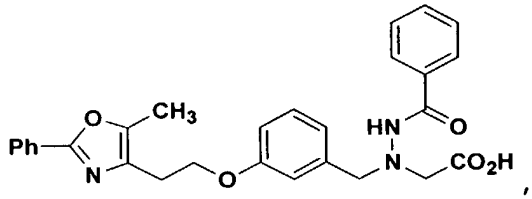
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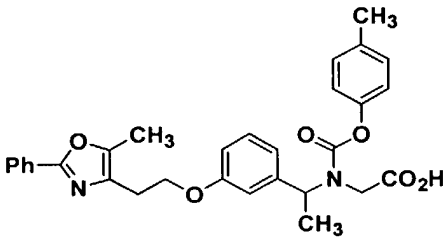
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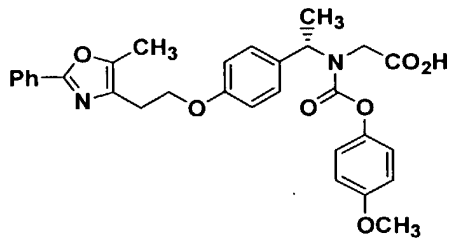
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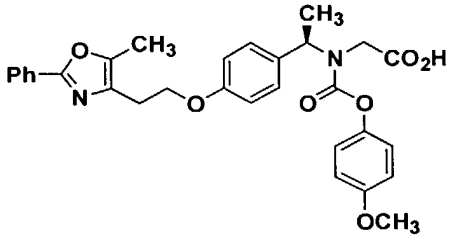
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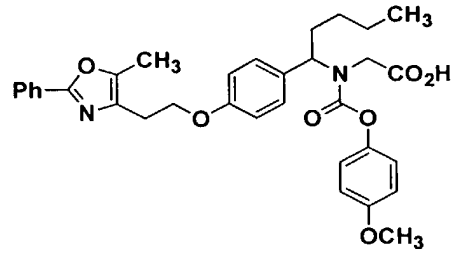
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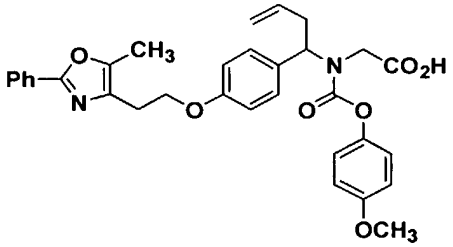
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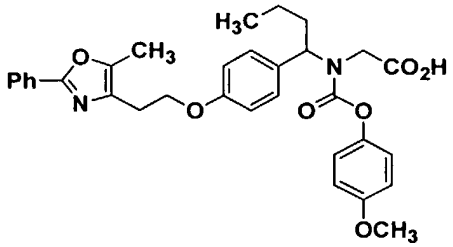
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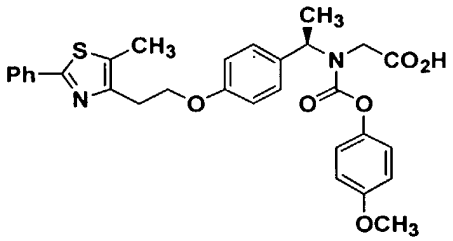
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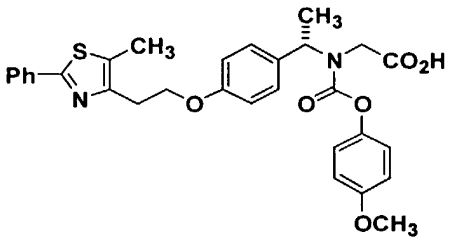
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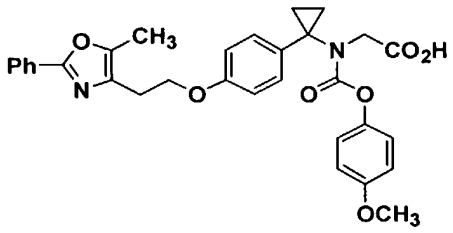
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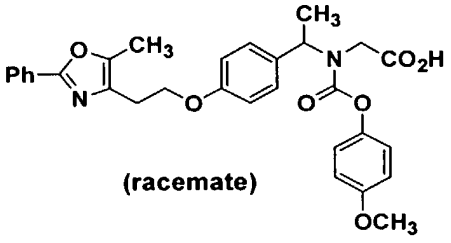
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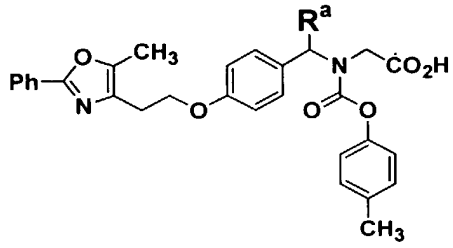
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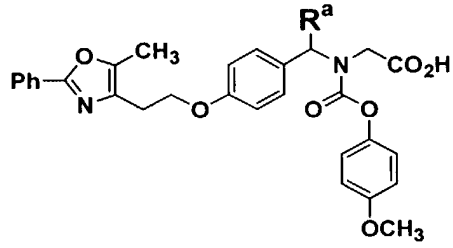
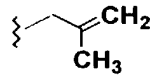
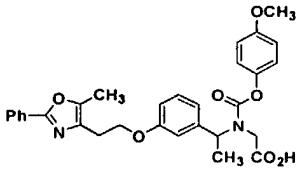

, where R^a = (±) Et, (±) i-Bu,
(±)  [.]



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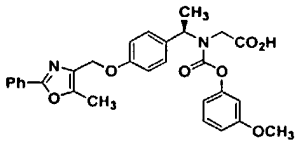

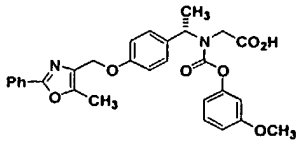

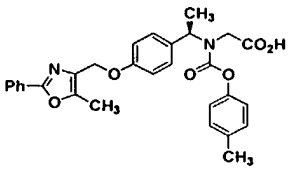

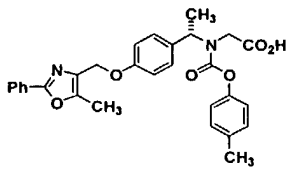

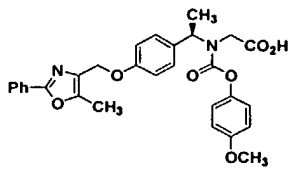

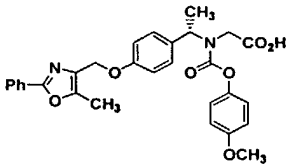

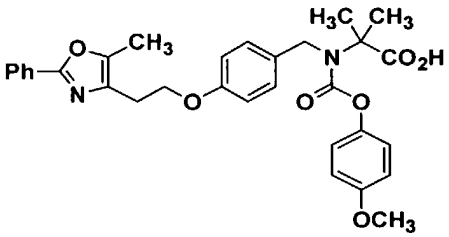

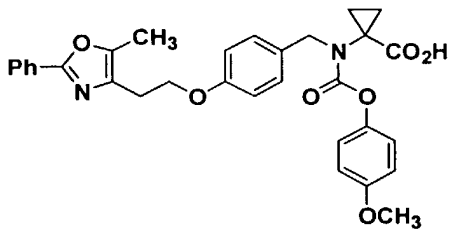

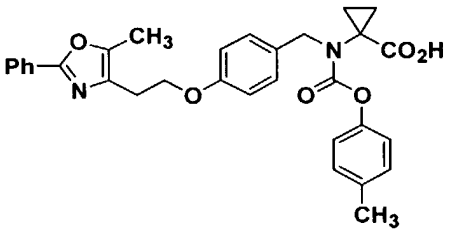

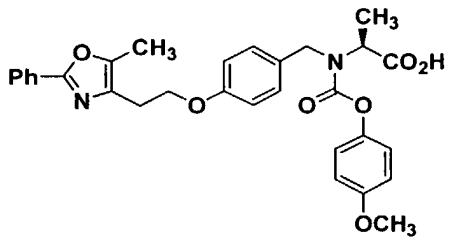

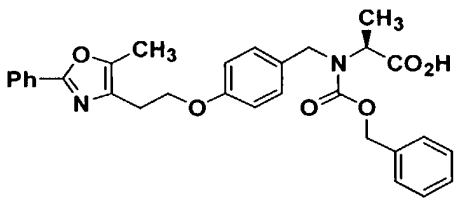

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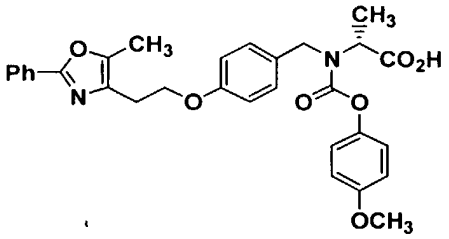

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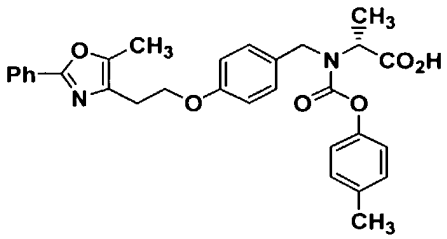

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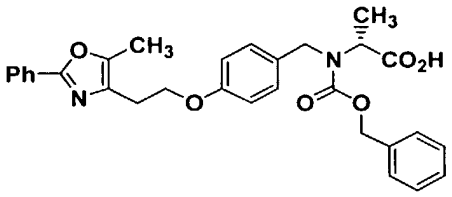

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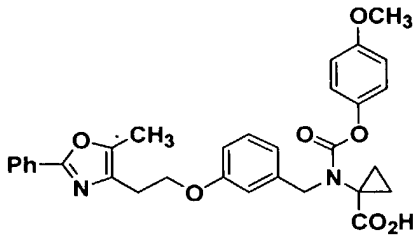

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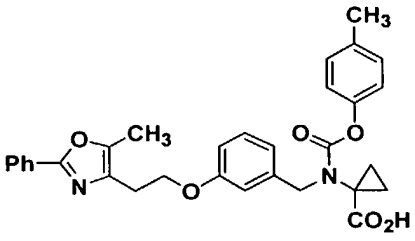

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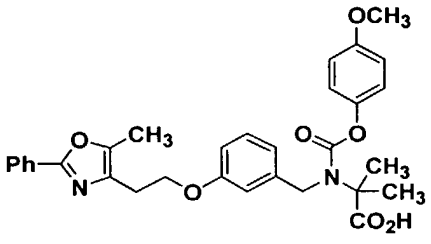

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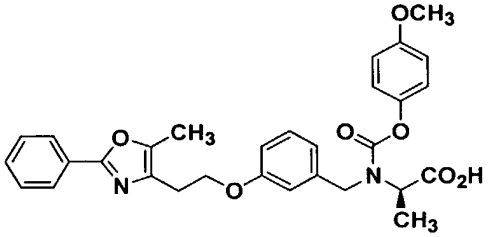

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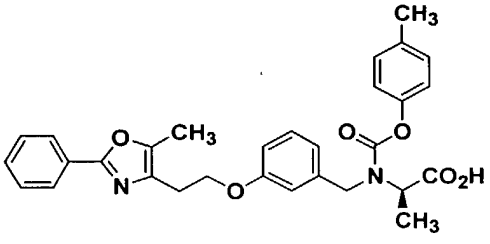

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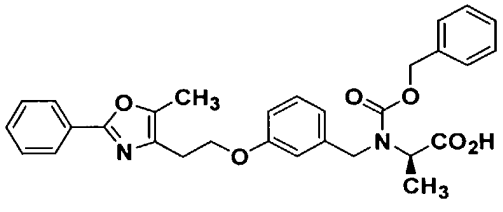

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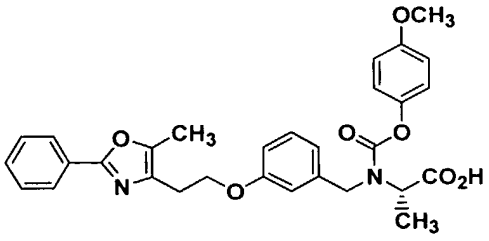

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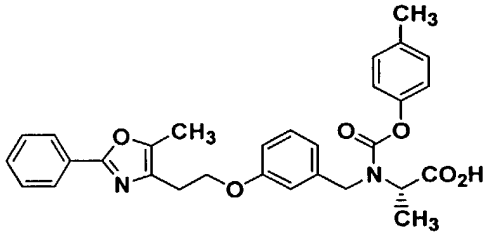

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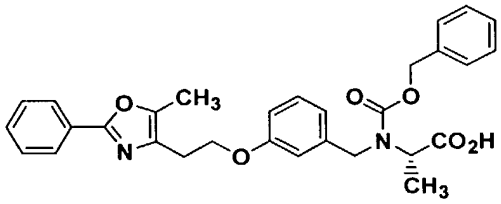

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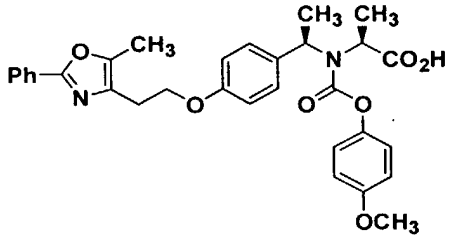

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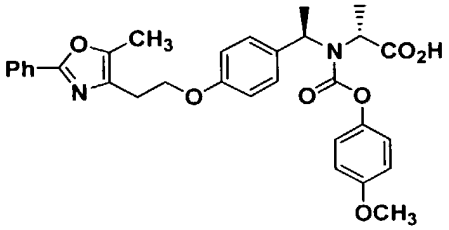

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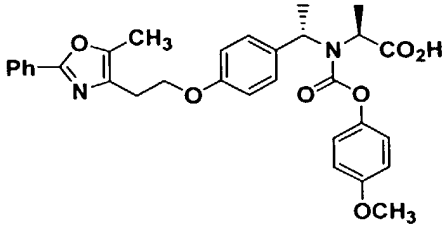

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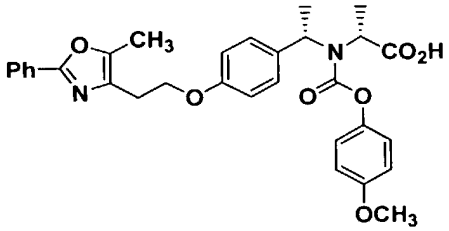

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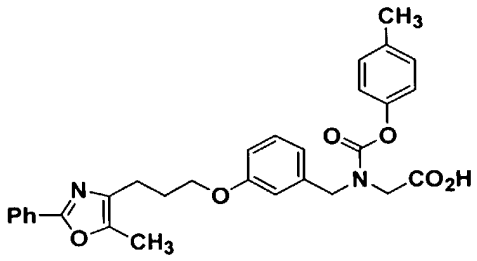

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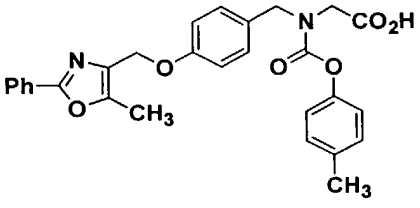

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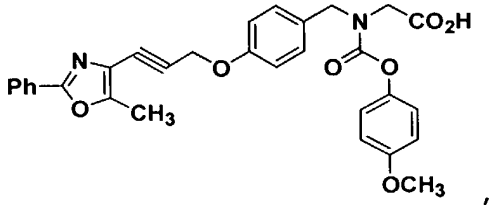

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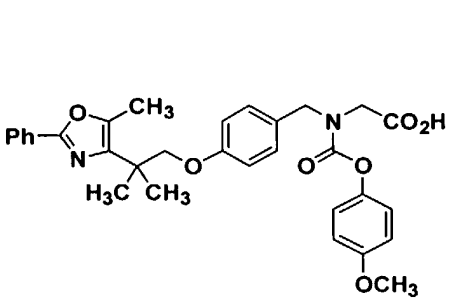
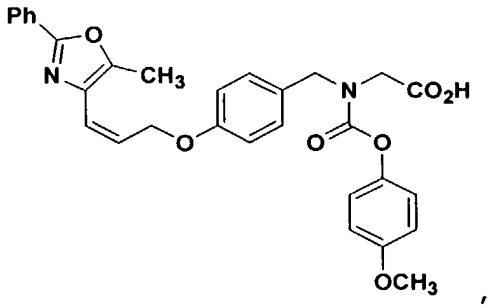
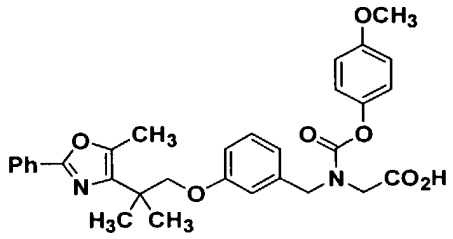
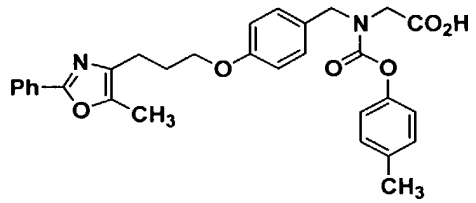
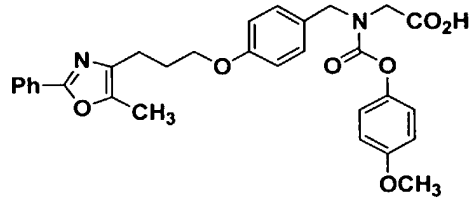
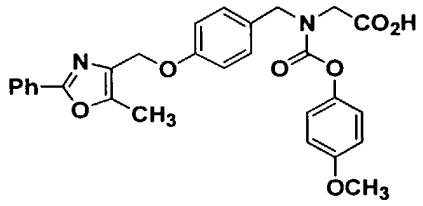
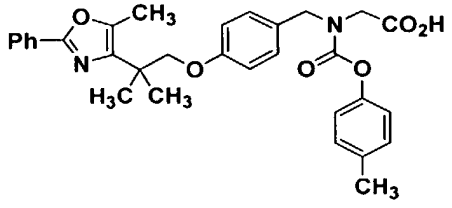
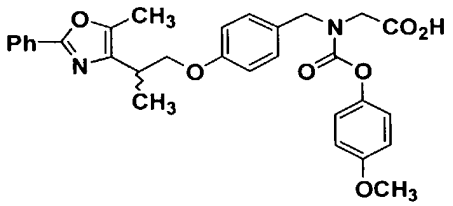
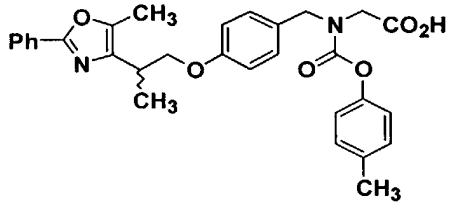

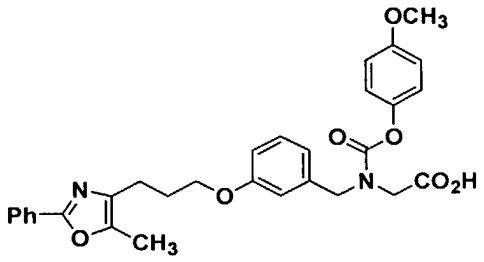

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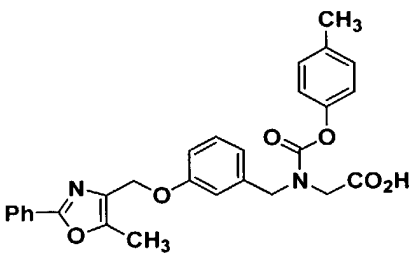

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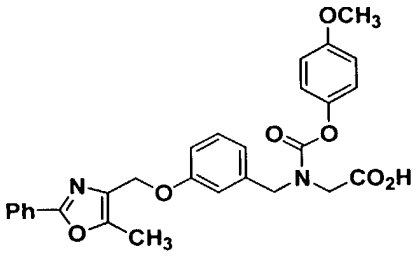

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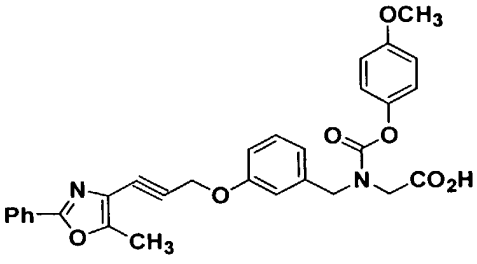

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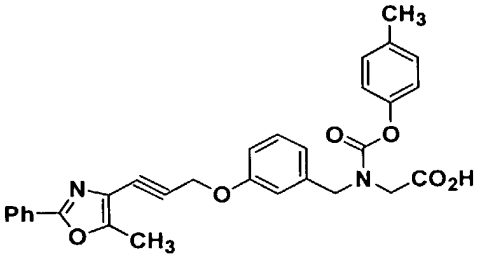

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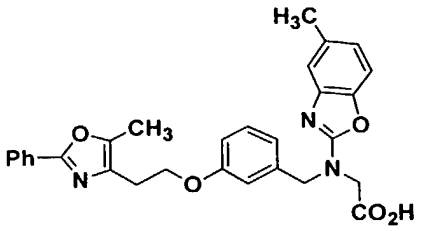

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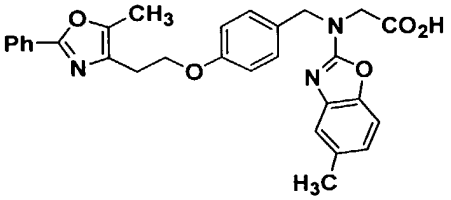

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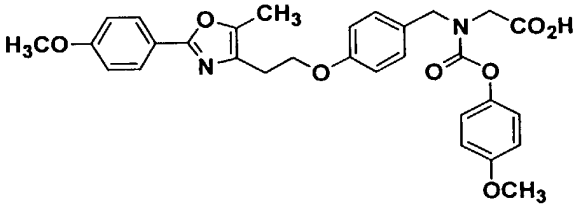

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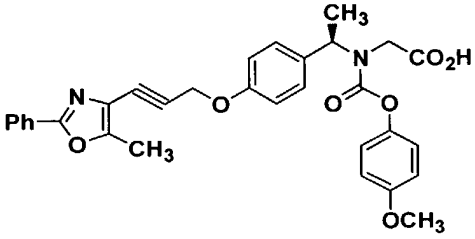

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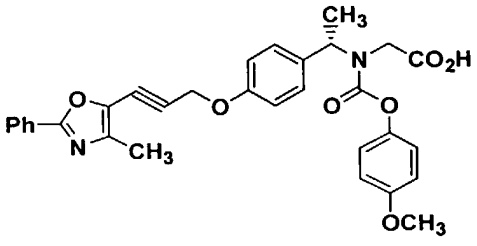

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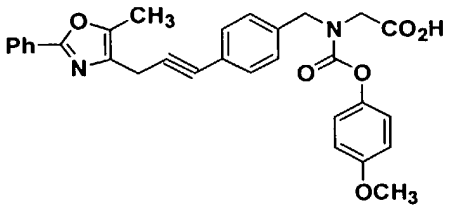
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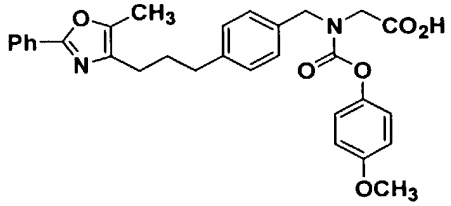
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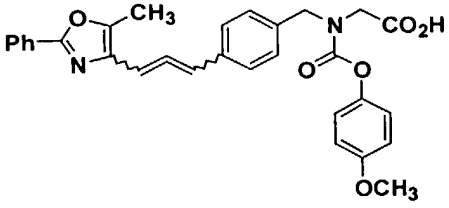
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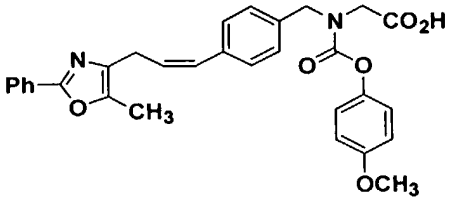
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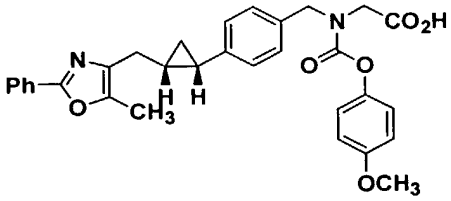
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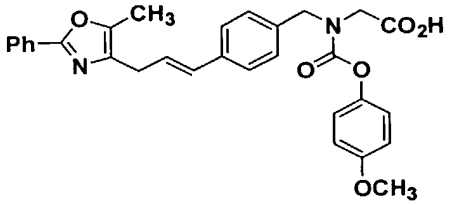
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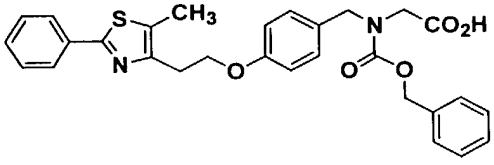
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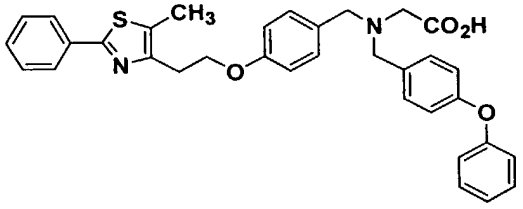
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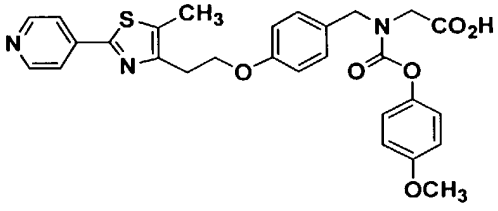
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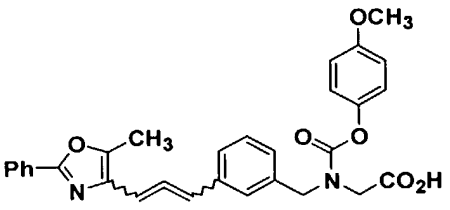
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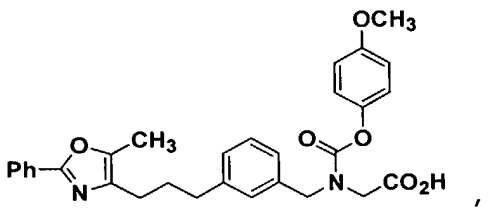
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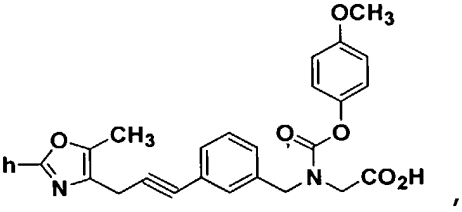
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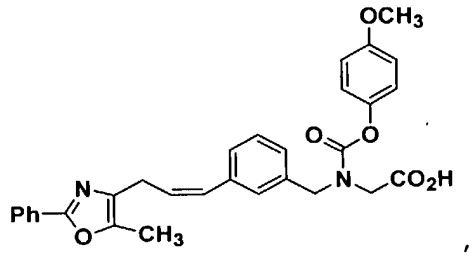
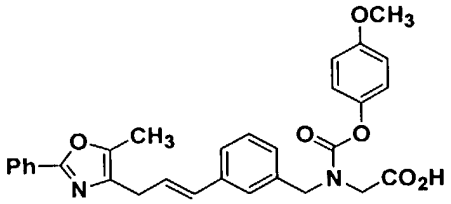
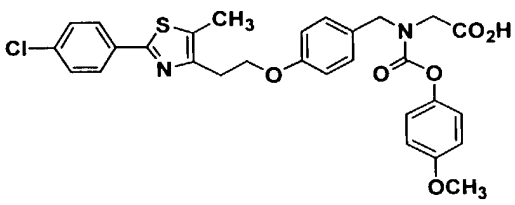
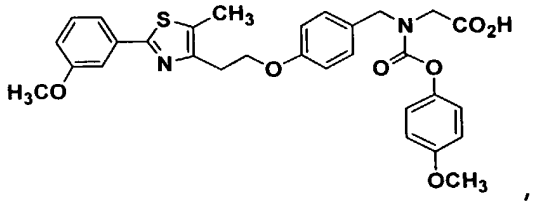
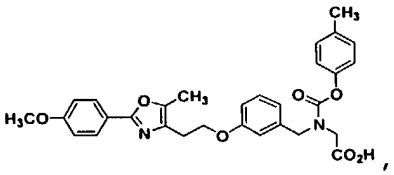
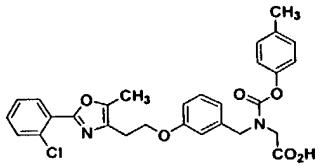
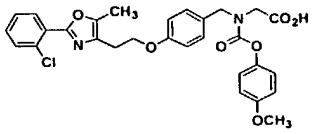
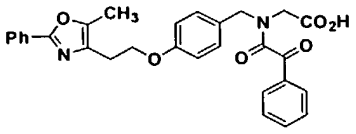
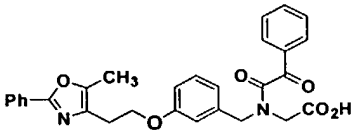
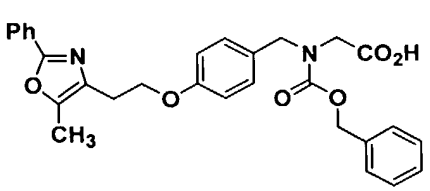
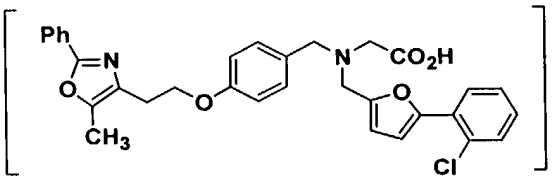
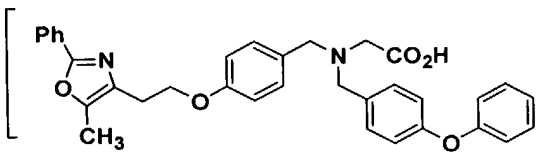
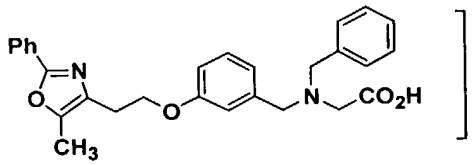










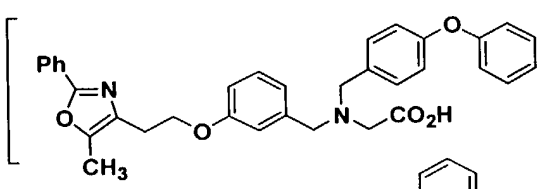
--17. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has [having] the structure

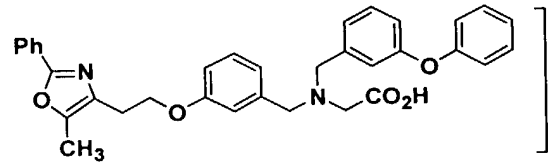


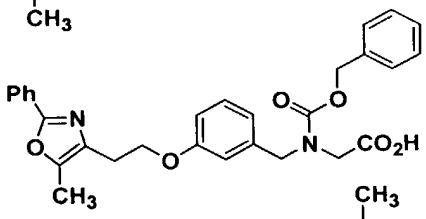


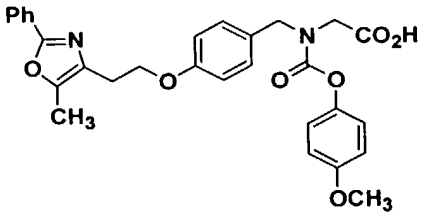


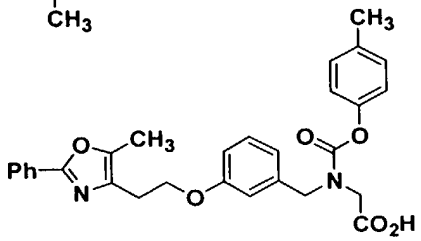


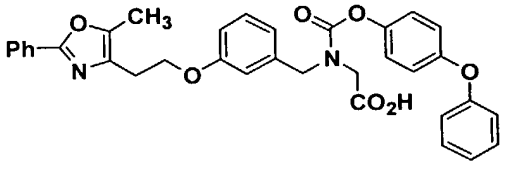


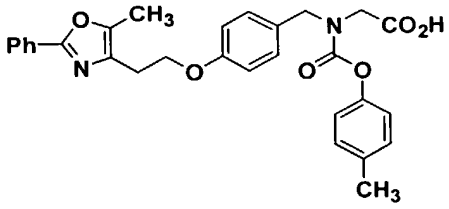


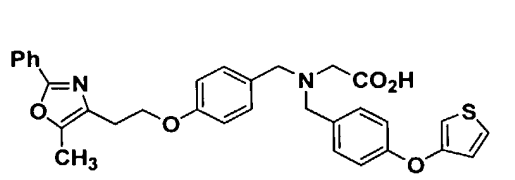


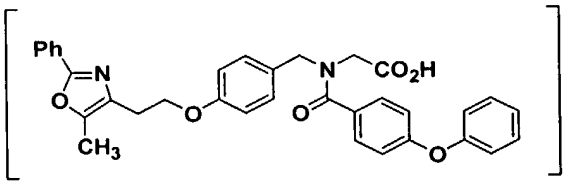


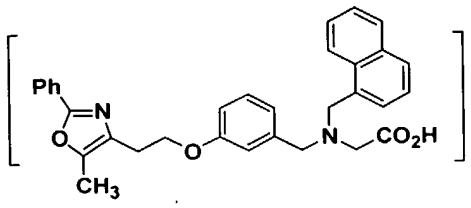


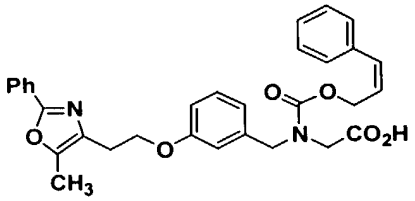


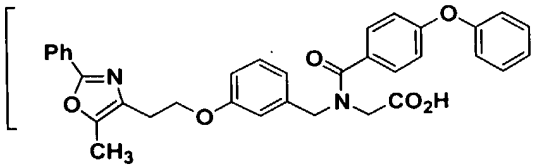


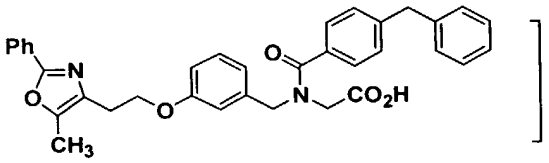


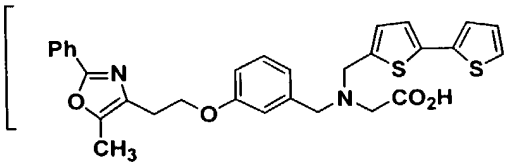


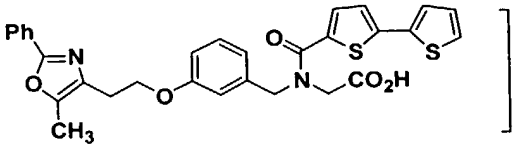


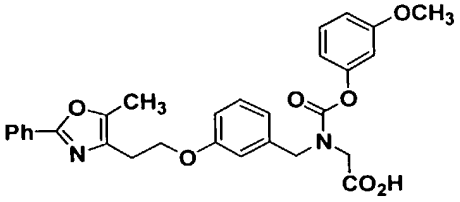


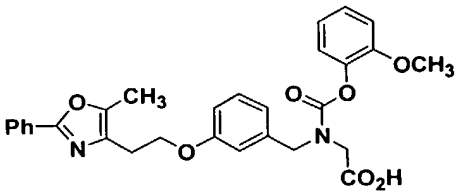


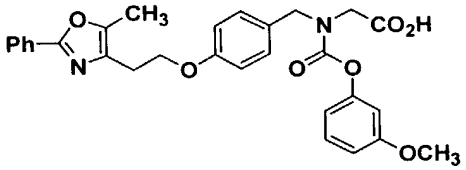


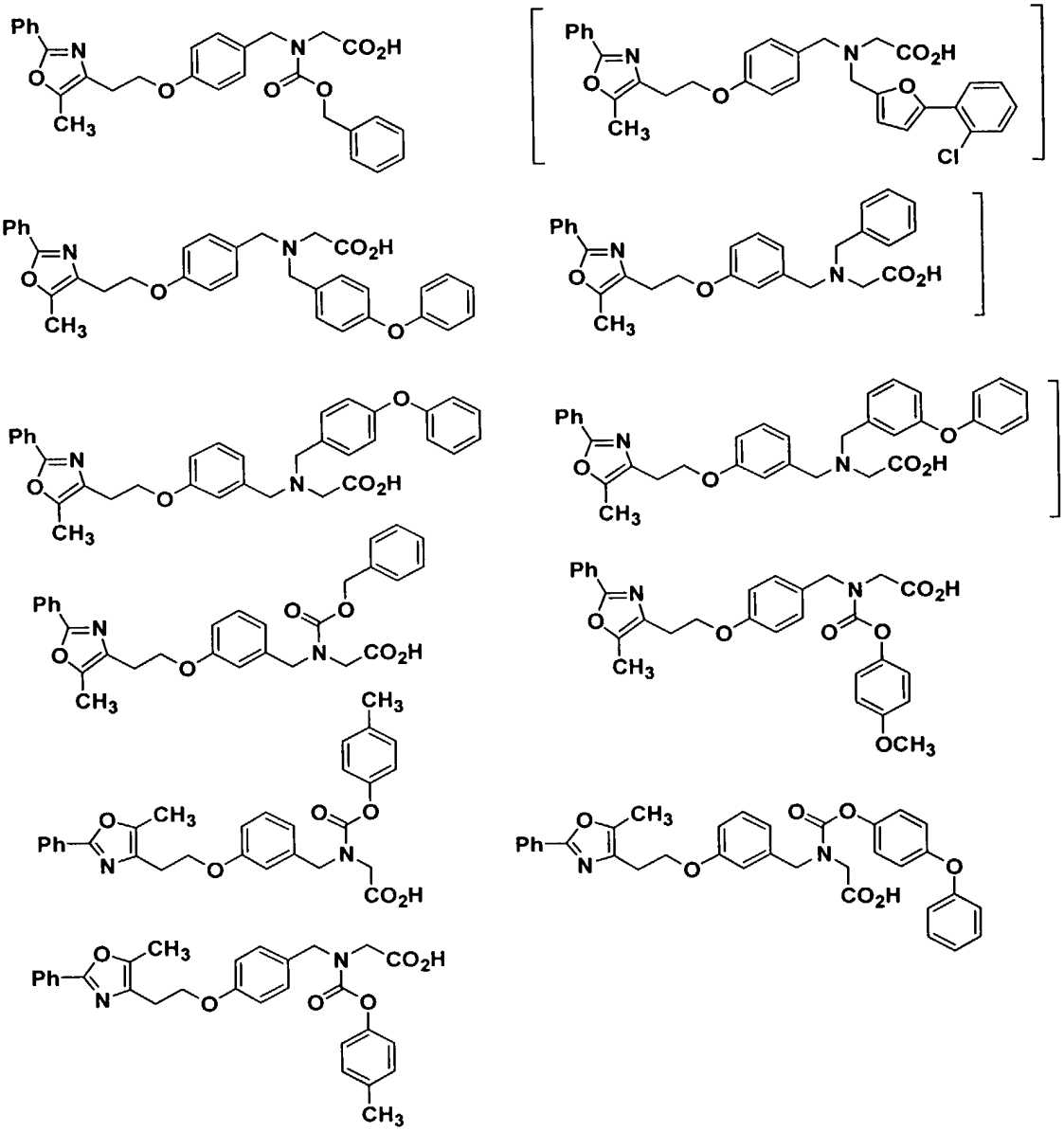


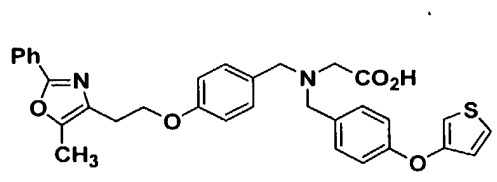


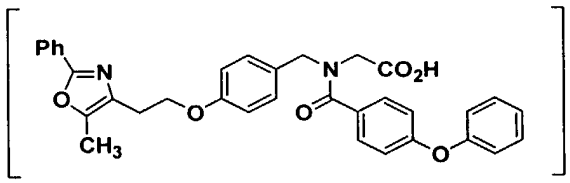


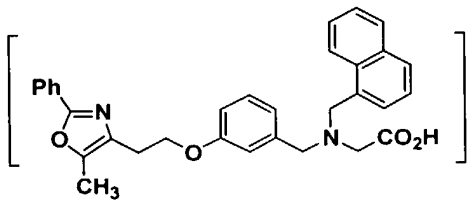


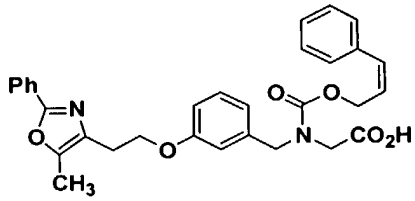


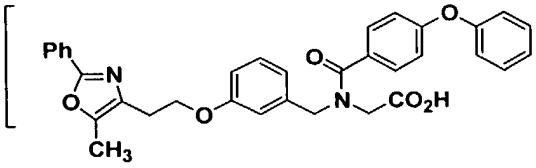


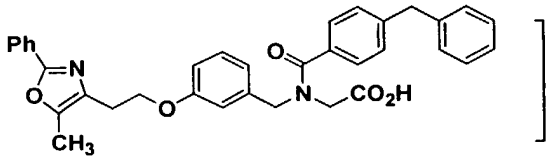


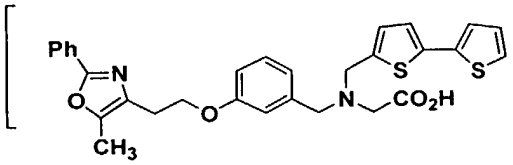


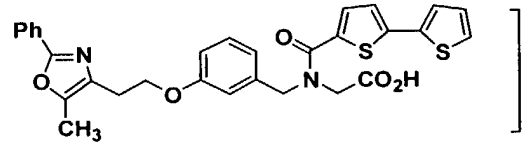


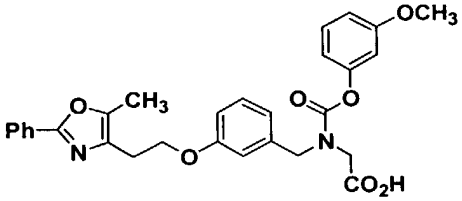


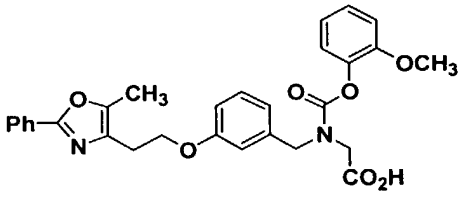


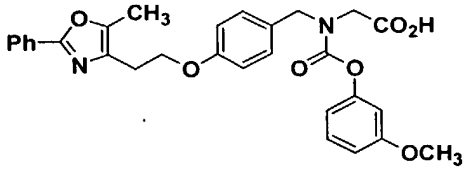


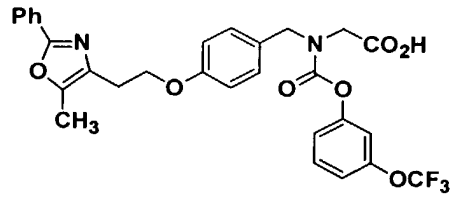


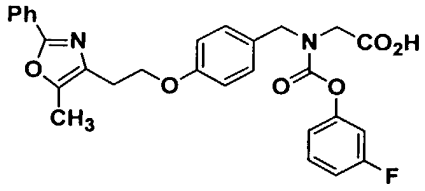


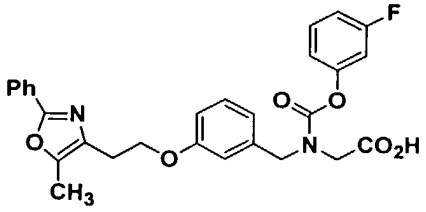


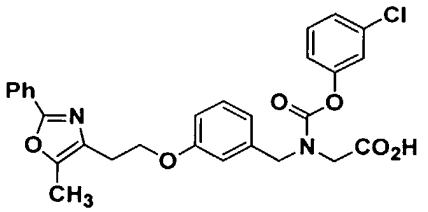


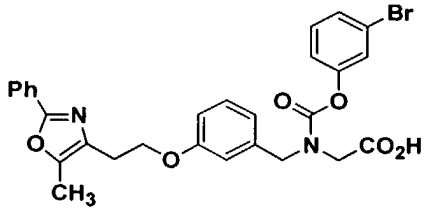


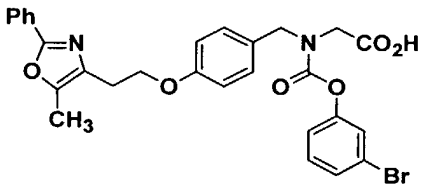


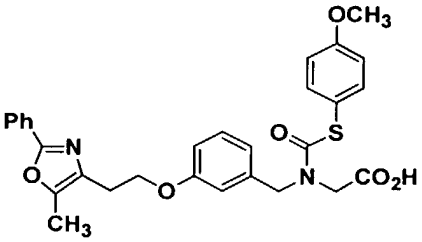


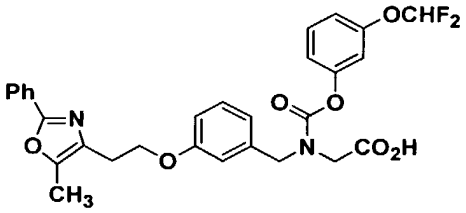


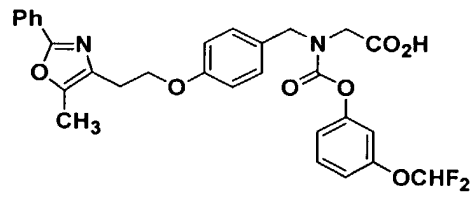


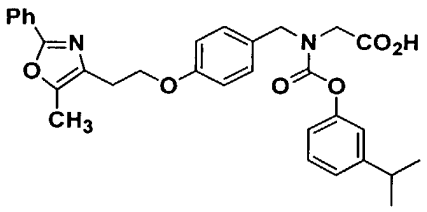


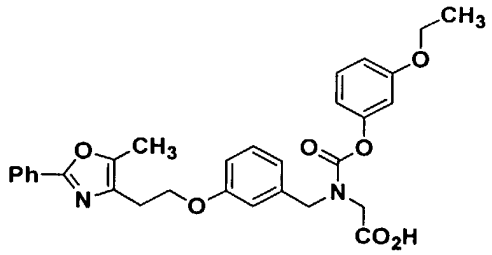


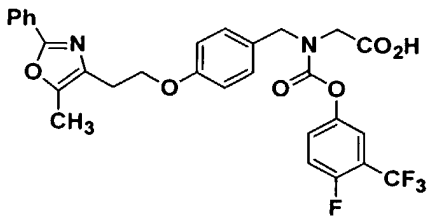


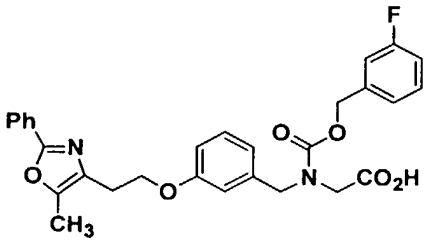


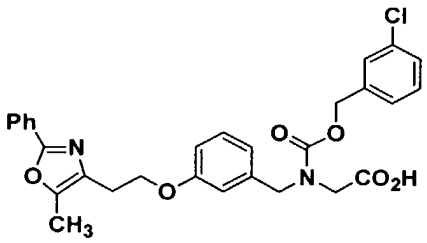


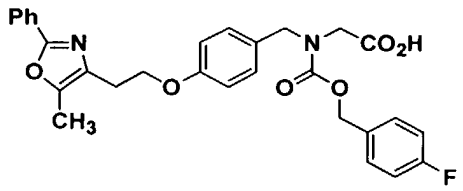


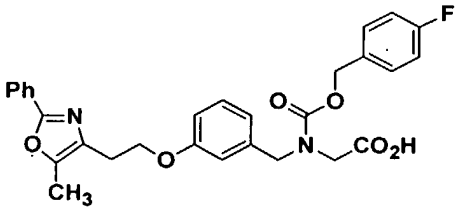


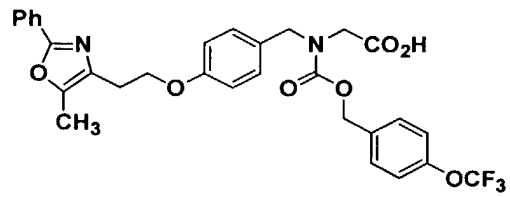


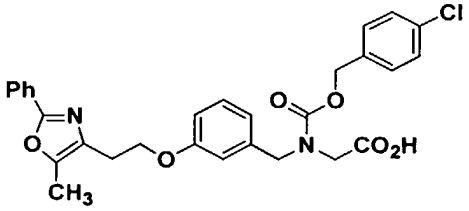


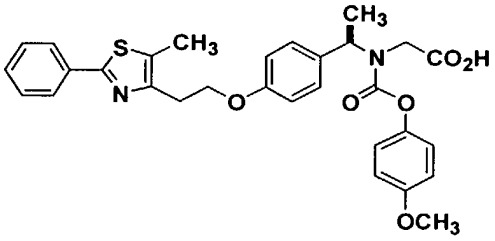


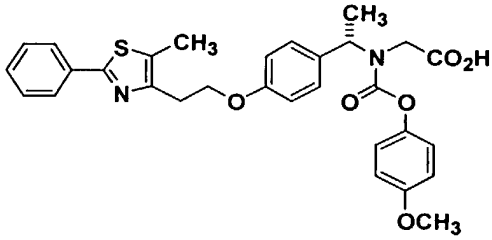


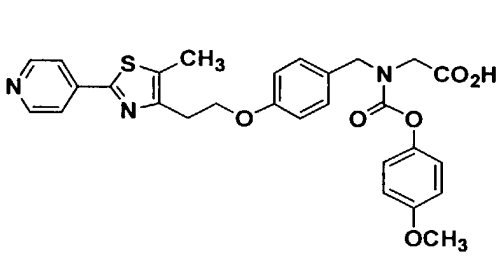












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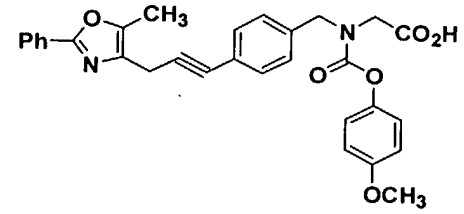
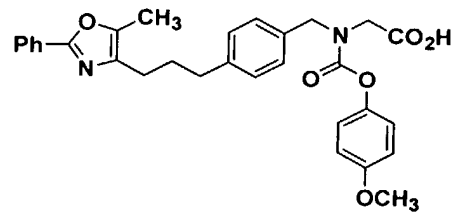
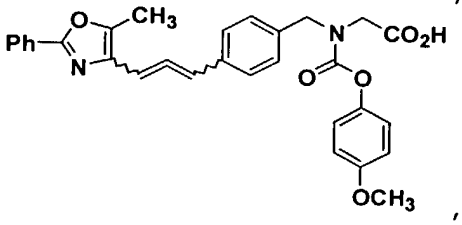
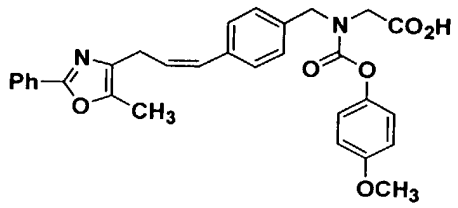
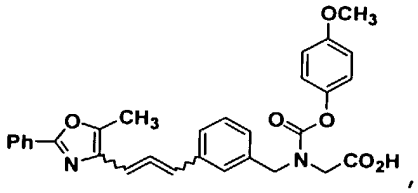
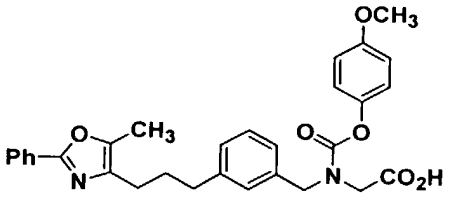
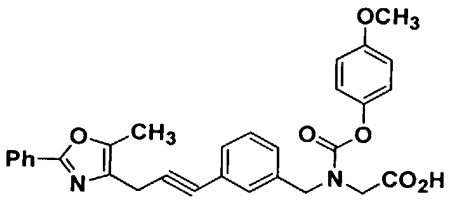
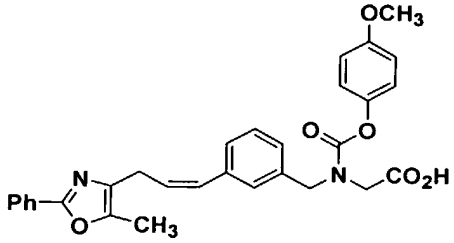
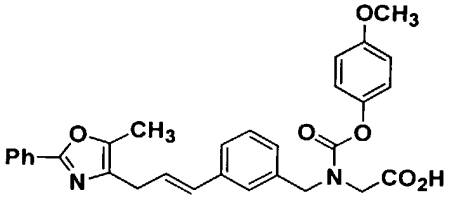
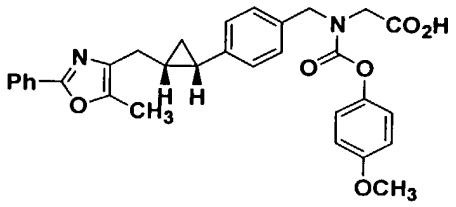
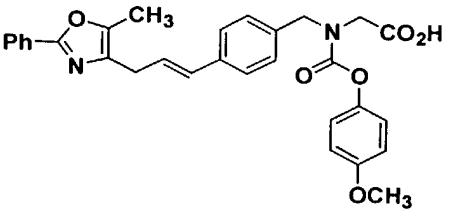
18. The [compound] method as defined in Claim 34 [1 having] wherein the compound employed has the structure

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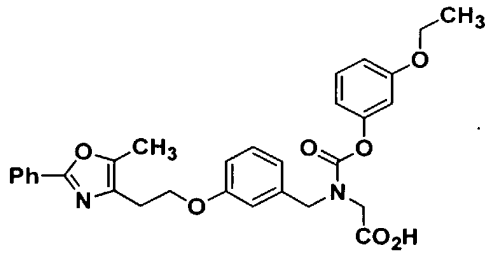
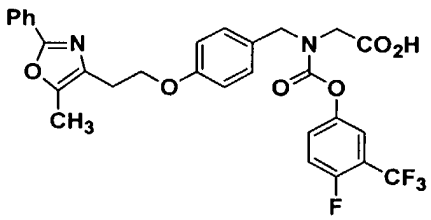
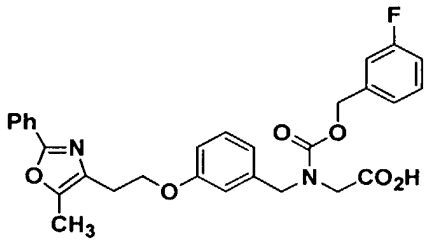
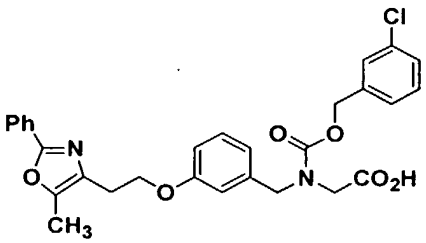
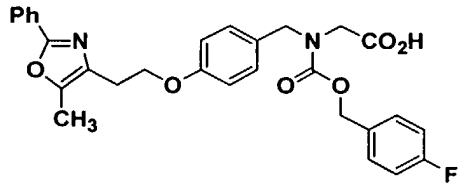
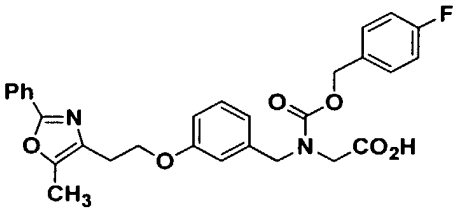


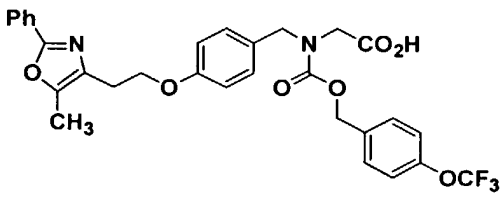


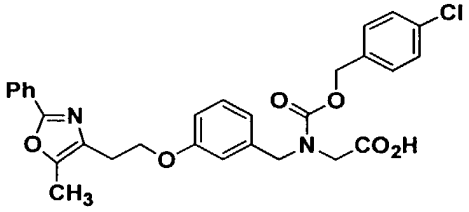


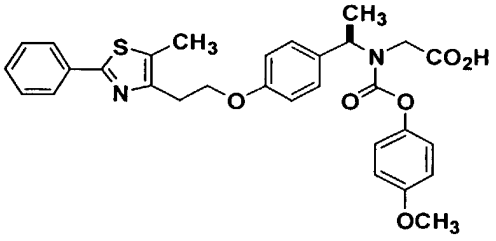


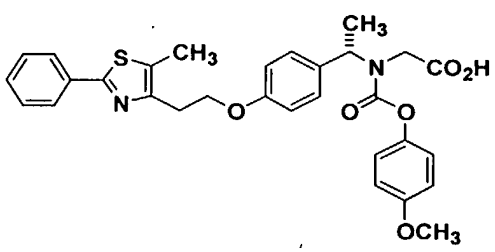


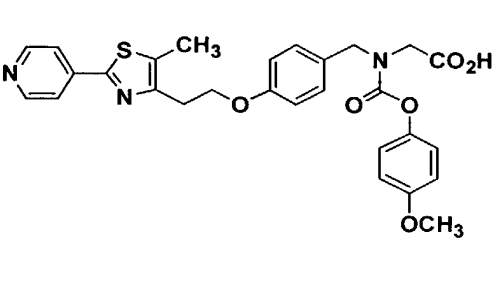




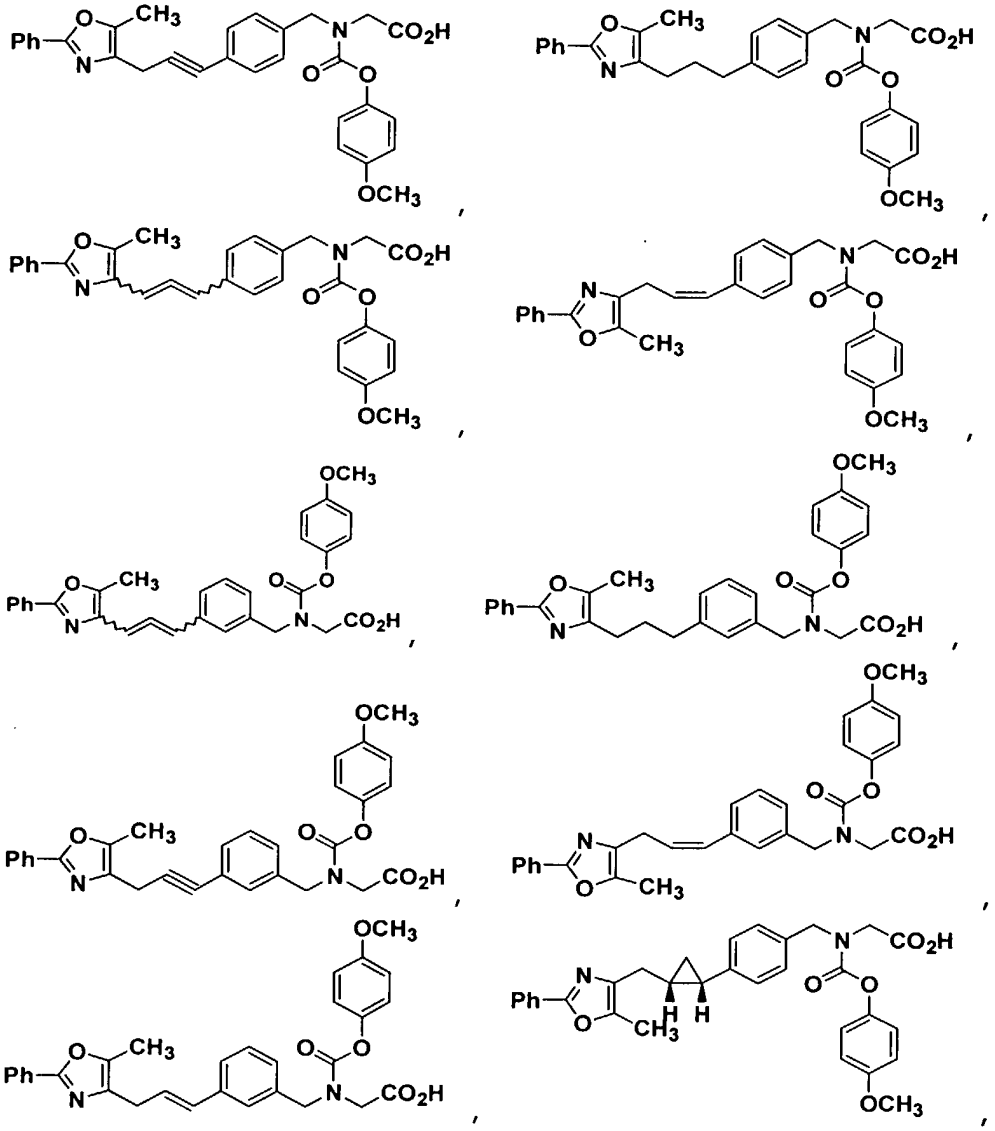


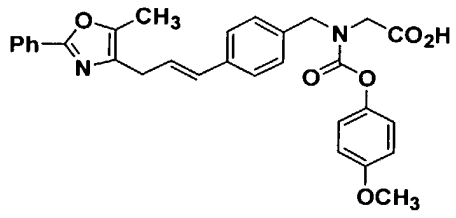






18. The [compound] method as defined in Claim 34 [1 having] wherein the compound employed has the structure





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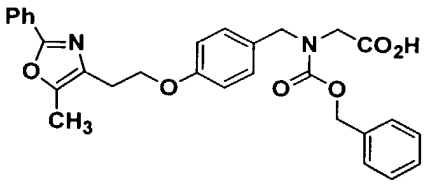
--20. (Amended) The [compound] method as defined in Claim [1] 34 wherein the compound employed has [having] the structure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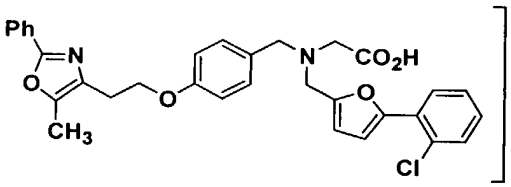
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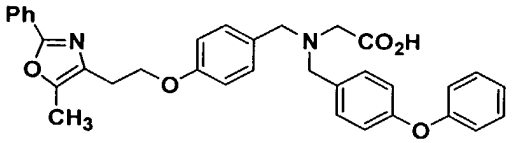
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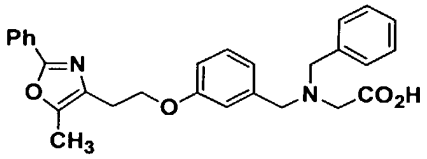

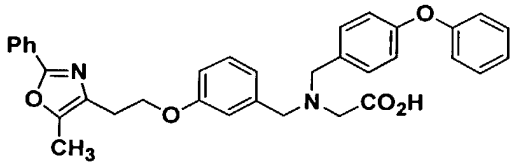
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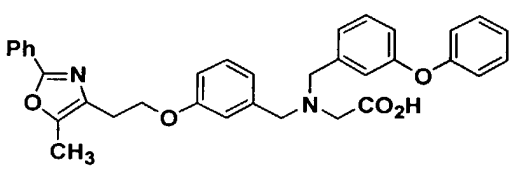
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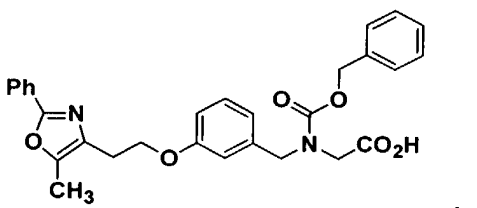
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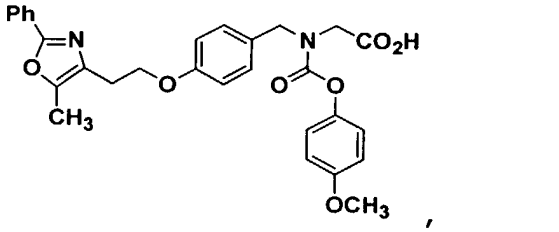
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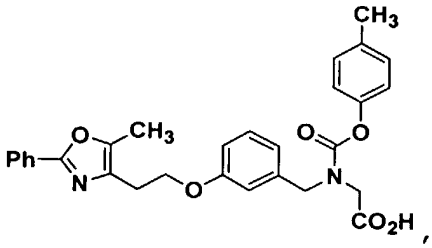

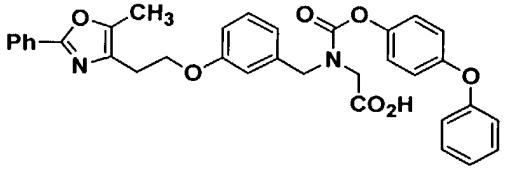

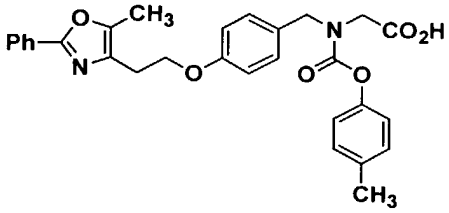

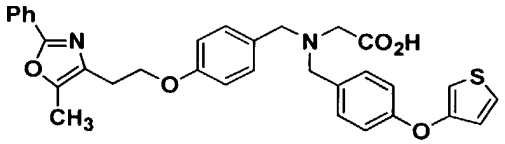

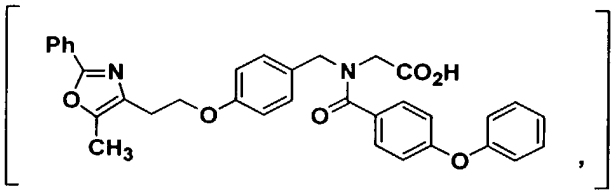

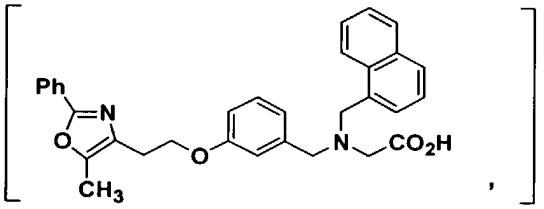

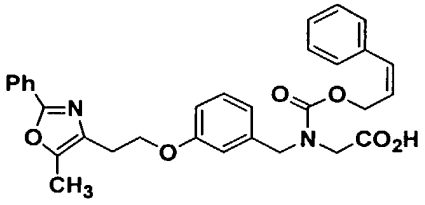

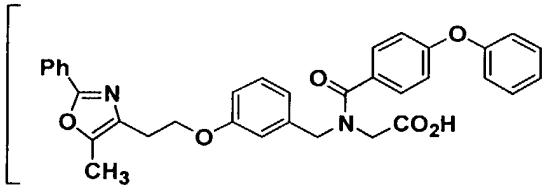

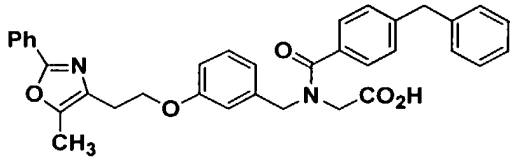

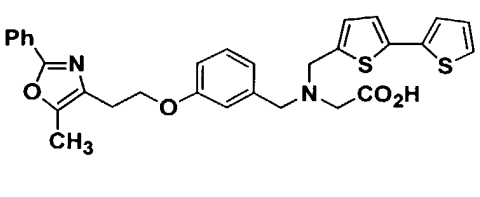

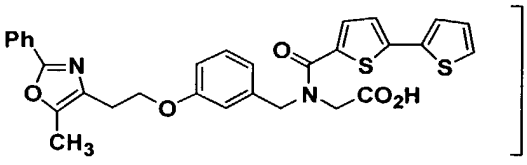

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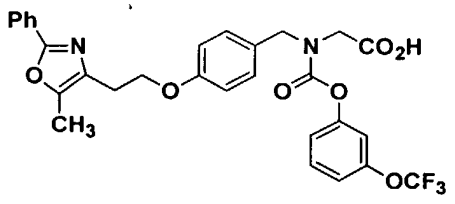

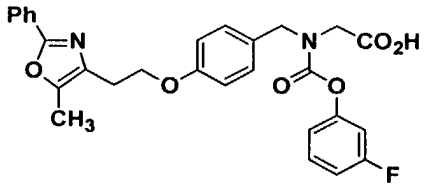

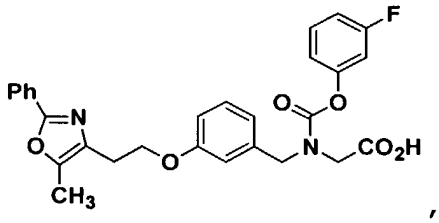

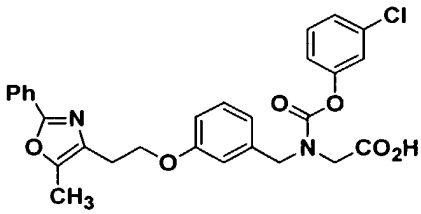

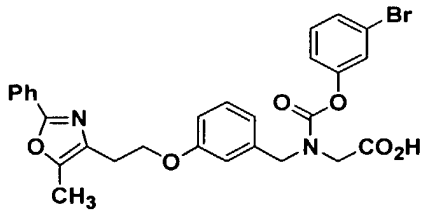

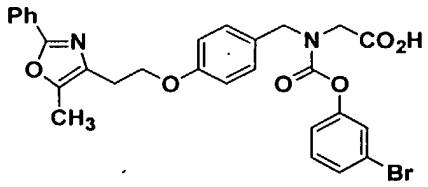

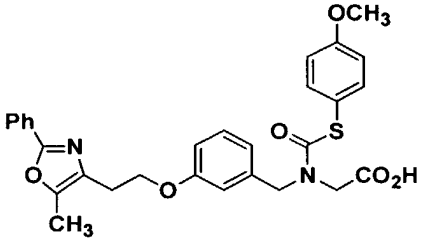

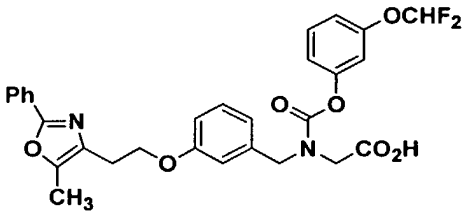

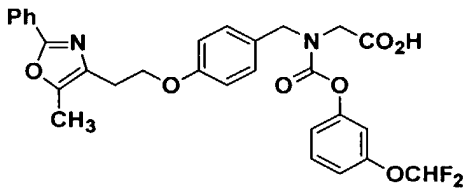

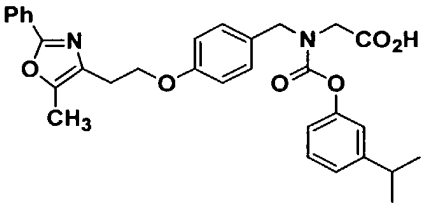

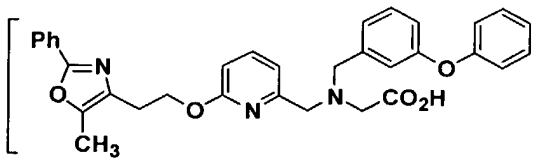

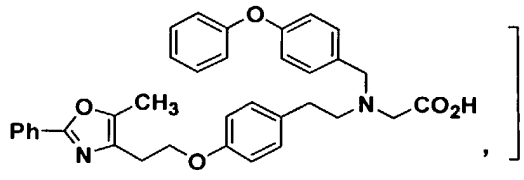

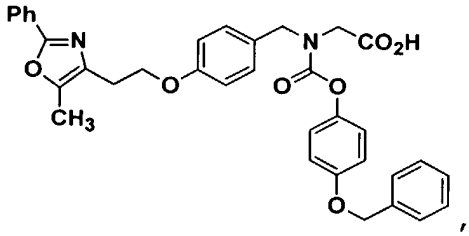

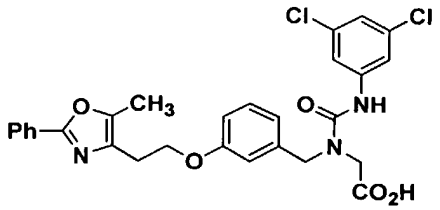

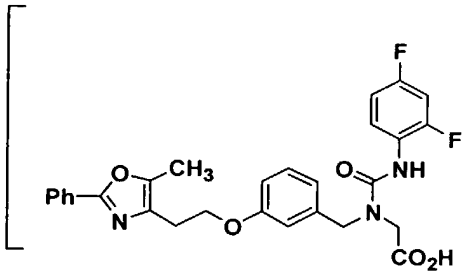

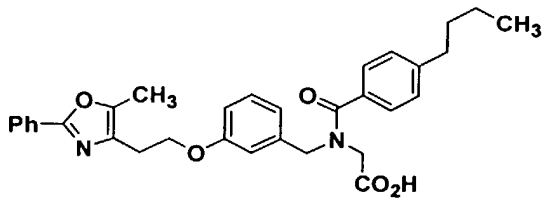

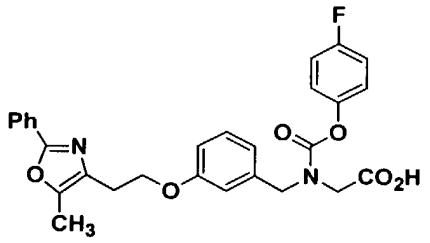

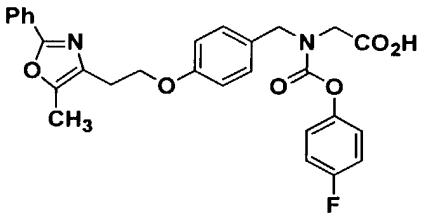

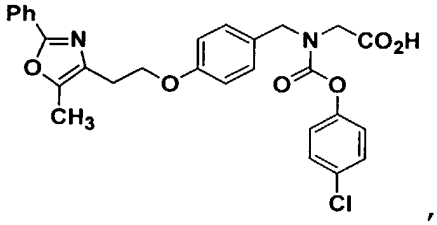

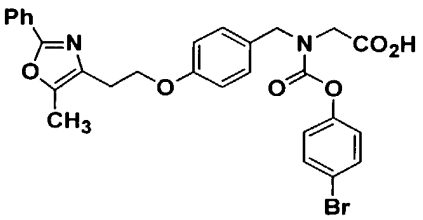

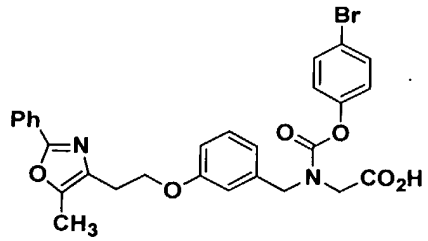
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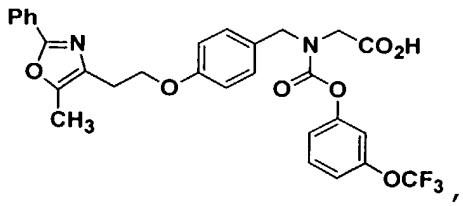
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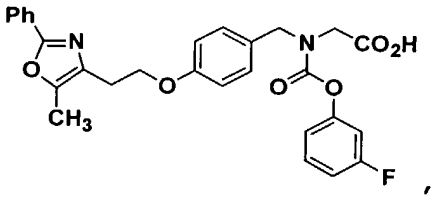
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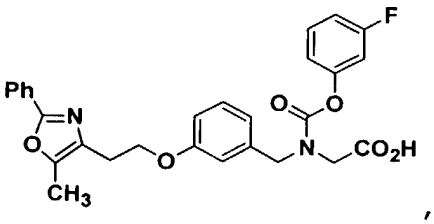
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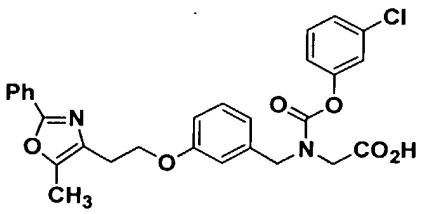
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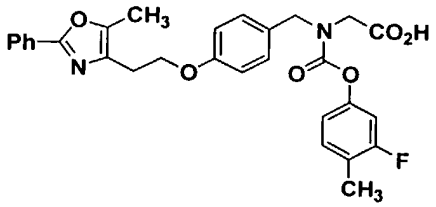

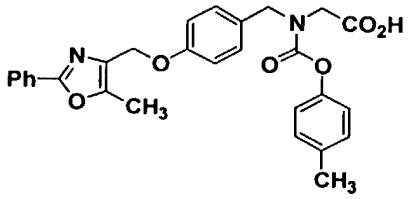

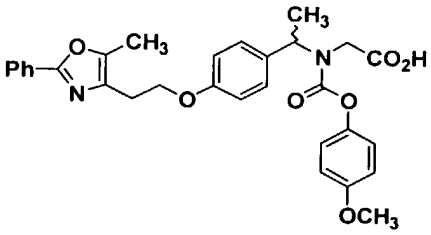

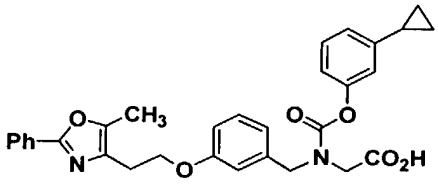

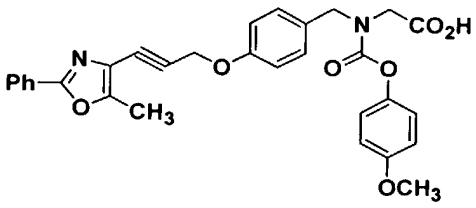

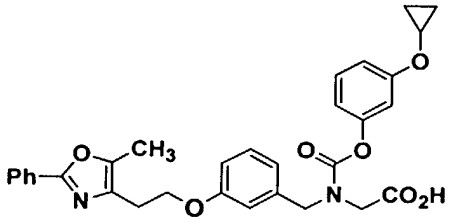

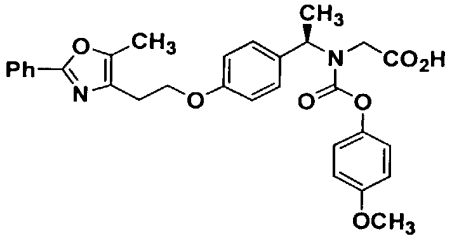

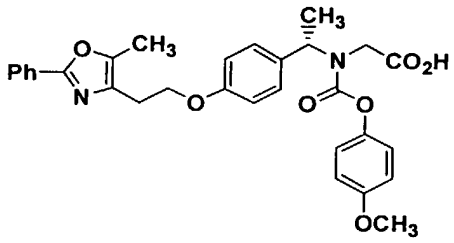

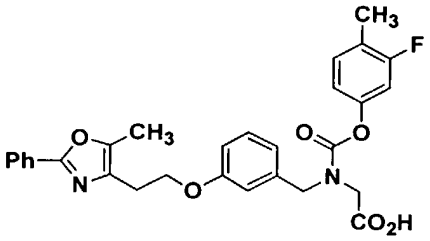

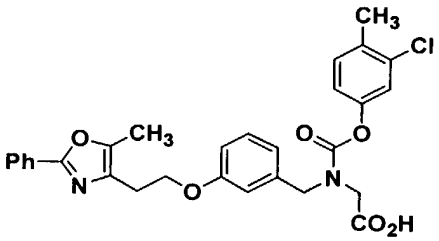

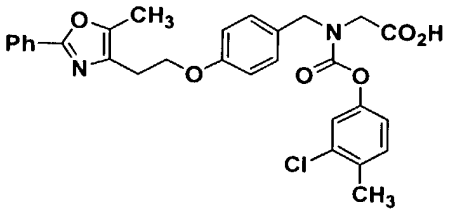

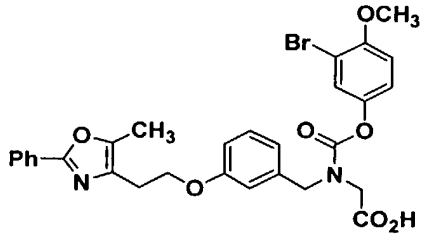

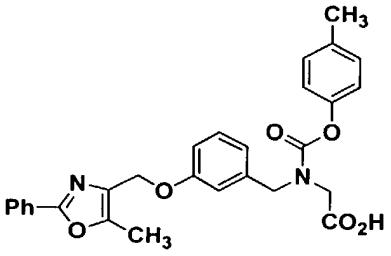

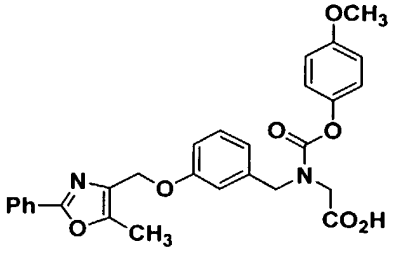

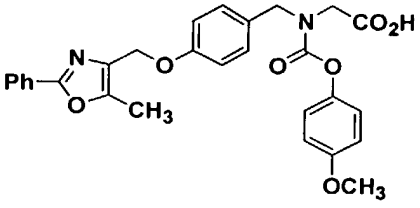

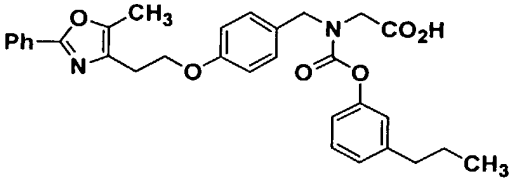

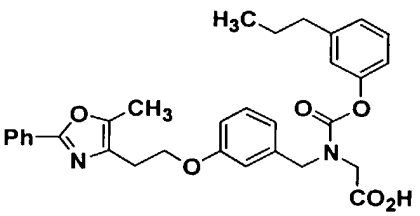

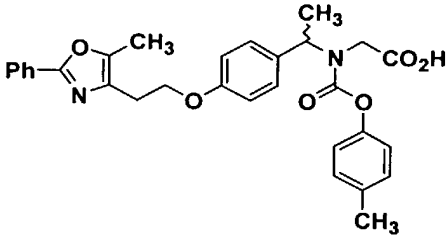

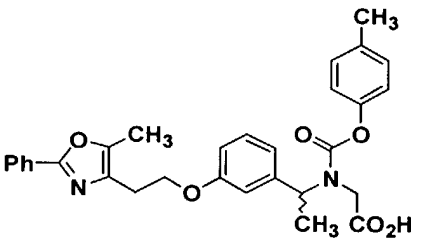

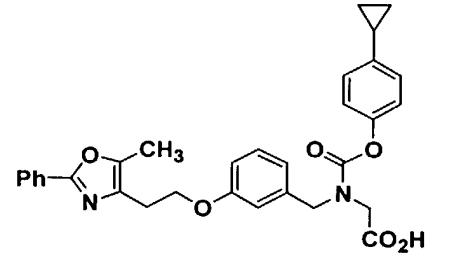

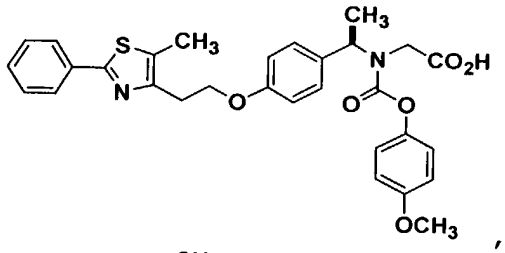

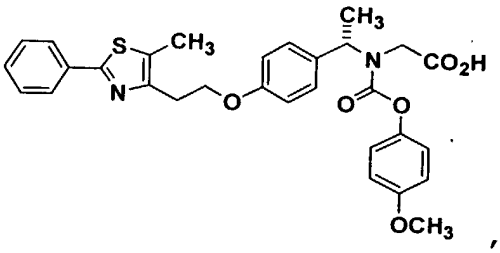

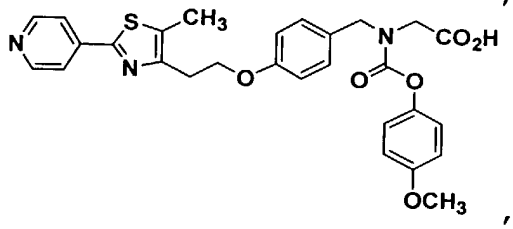

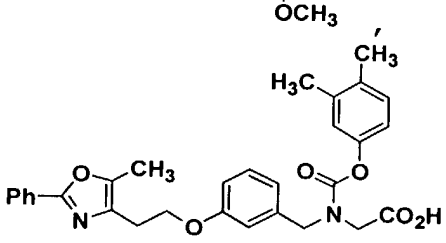

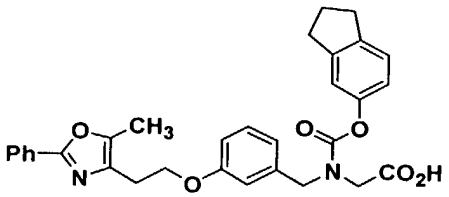

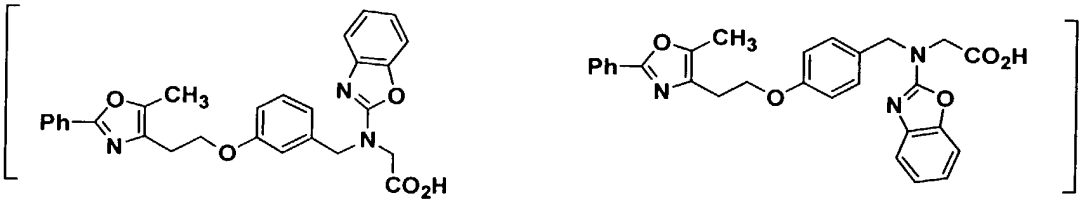

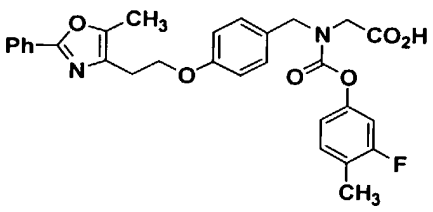

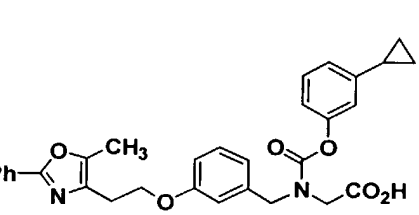

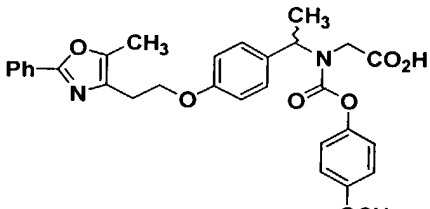

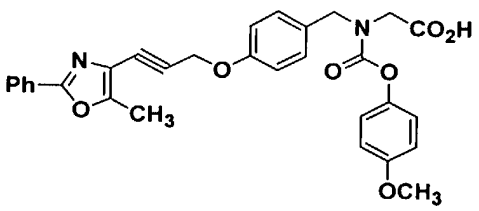

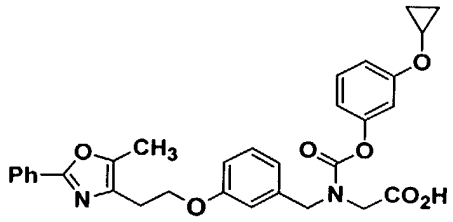

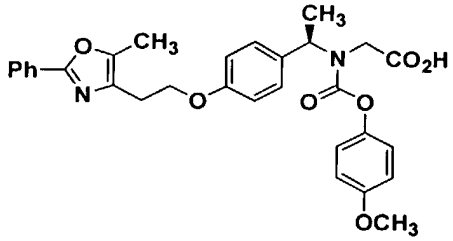

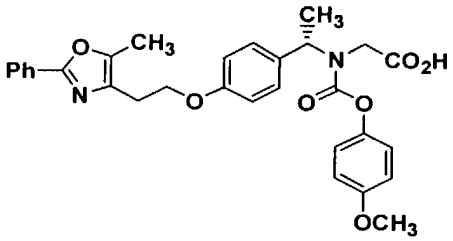

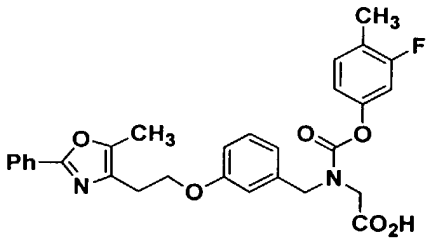

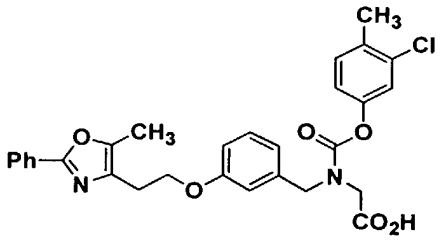

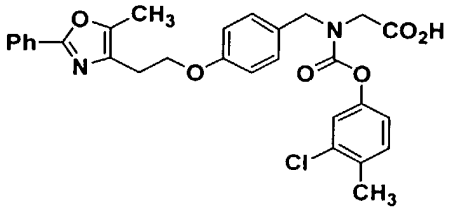

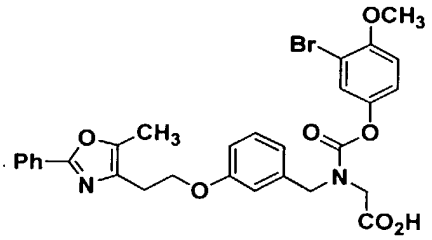

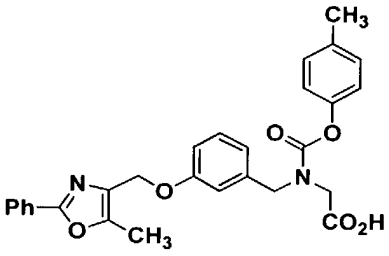

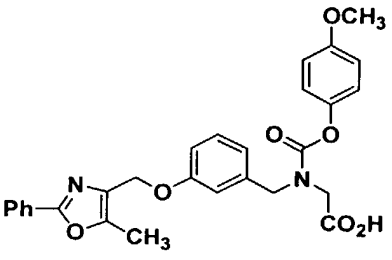

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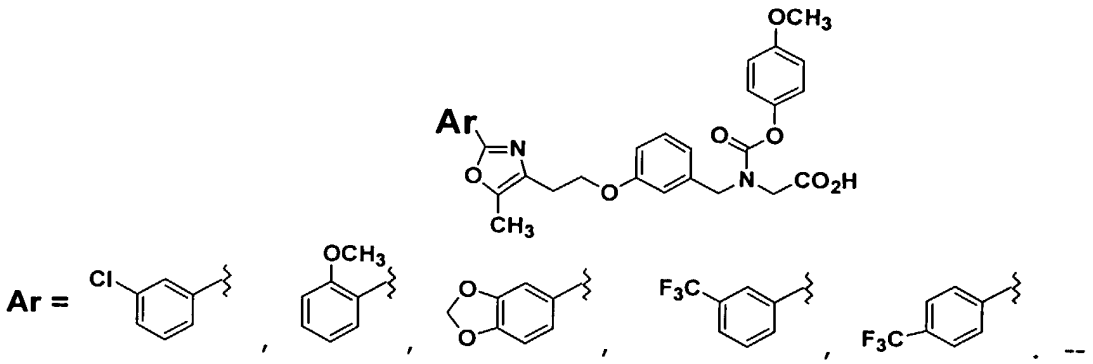
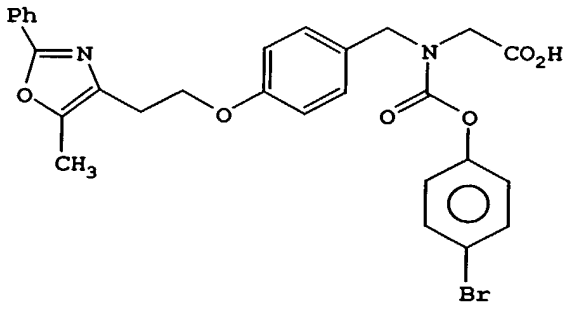
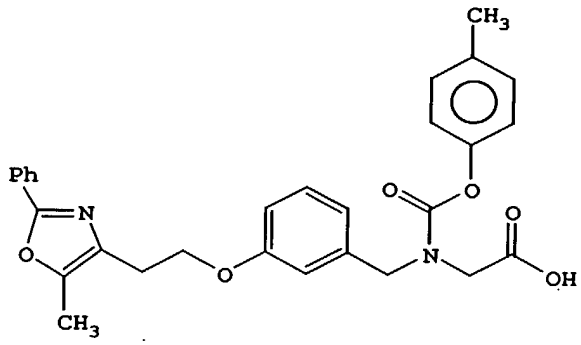


--21. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--22. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



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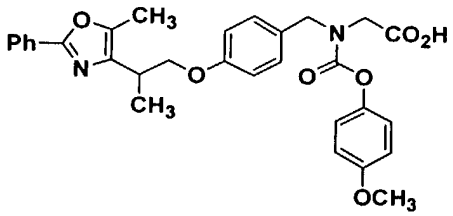
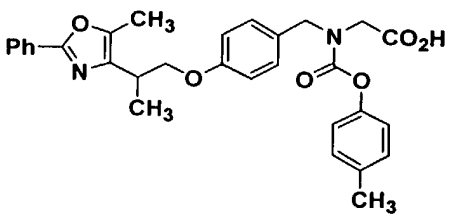
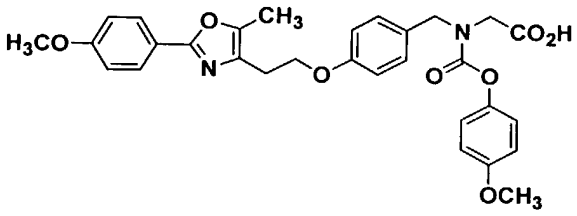
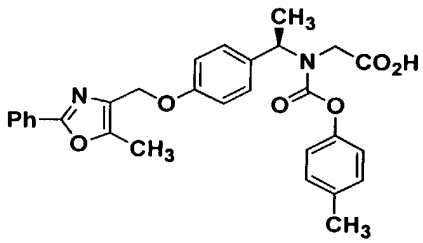
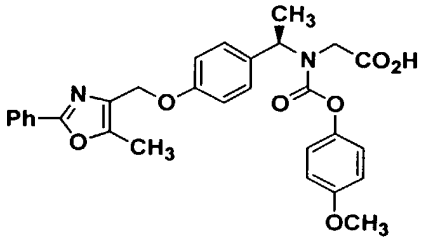
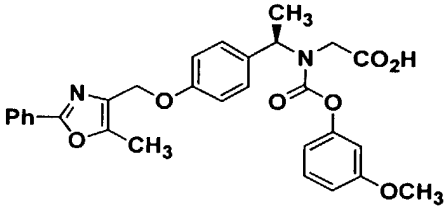


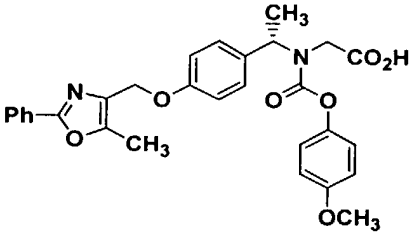


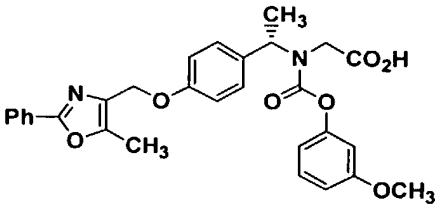


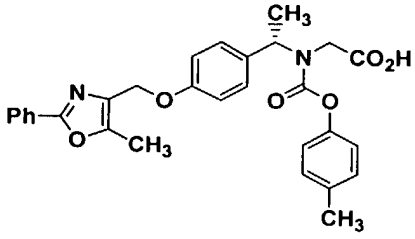


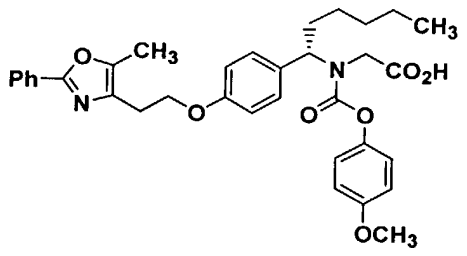
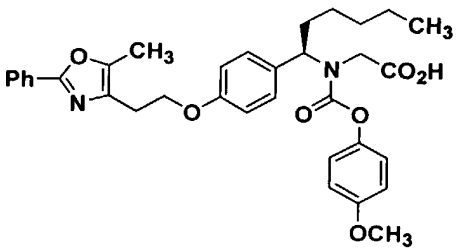
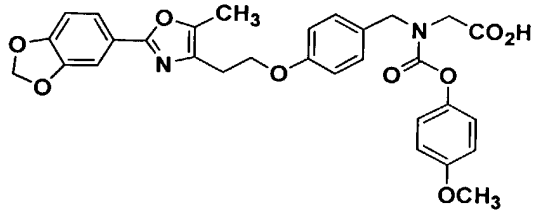
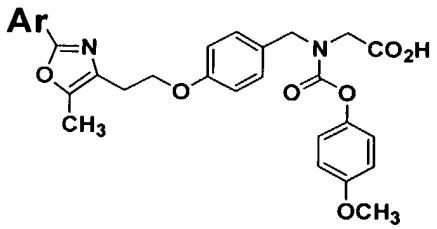
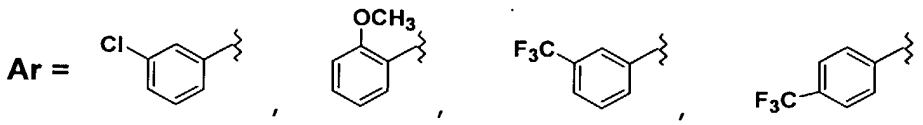
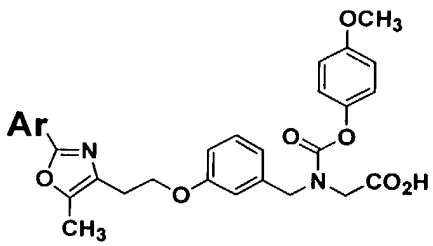
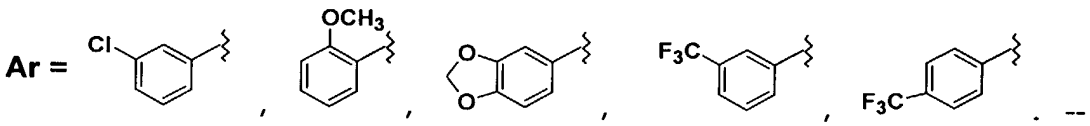






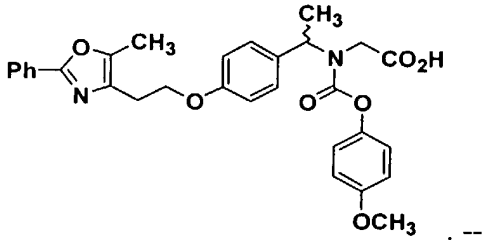




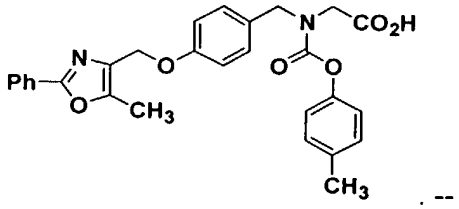








--21. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure

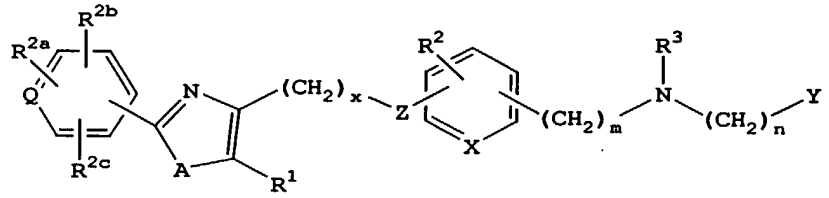
--31. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--32. (Amended) The [compound] method as defined in Claim [1 having] 55 wherein the compound employed has the structure



--34. (Amended) A method for lowering blood glucose levels or for treating diabetes, or for treating a premalignant disease, an early malignant disease, a malignant disease or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound [as defined in Claim 1] which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is CH;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

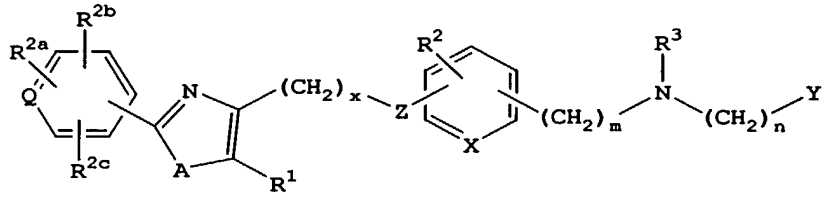
R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R^3 is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO_2R^4 were R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$ here R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $P(O)(OR^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--37. (Amended) A pharmaceutical combination comprising a compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is CH;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R^3 is aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkenyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylalkyloxycarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylalkoxycarbonyl, heteroarylalkyloxyarylalkyl, arylalkenylarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl or polyhaloalkylaryloxycarbonyl;

Y is CO_2R^4 were R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$ here R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $P(O)(OR^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof [as defined in Claim 1] and a lipid-lowering agent, a lipid modulating agent, an antidiabetic agent, an anti-obesity agent, an antihypertensive agent, a platelet aggregation inhibitor, and/or an antiosteoporosis agent. --

--39. (Amended) The combination as defined in Claim [38] 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT

inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β-adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

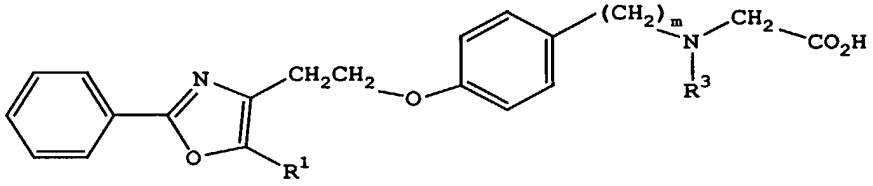
an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

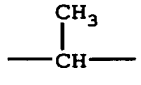
--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, [or] atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim [43] 37. --

New Claims 55 and 56 have been added as set out below.

55. A method for lowering blood glucose levels or for treating diabetes, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound which has the structure



where R^1 is alkyl,

$(CH_2)_m$ is CH_2 or  and R^3 is aryloxycarbonyl or alkoxyaryloxycarbonyl.

56. The method as defined in Claim 55 where in the compound employed $(CH_2)_m$ is CH_2.